Dietary fibre in the prevention of gastrointestinal inflammation and toxicity in patients undergoing pelvic radiotherapy for cancer

Wedlake, Linda Jane

Awarding institution:
King's College London

Dietary fibre in the prevention of gastrointestinal inflammation and toxicity in patients undergoing pelvic radiotherapy for cancer

A thesis submitted for the degree of

Doctor of Philosophy

in

Nutritional Sciences

Linda J Wedlake

2015

King's College London

School of Medicine

Diabetes and Nutritional Sciences Division

Abstract

Introduction

Approximately 17,000 patients a year receive radiotherapy for the pelvic cancers. Acute radiation-induced damage to normal non-cancerous tissues (toxicity) is characterised by an inflammatory response which has many pathophysiological similarities to inflammatory bowel disease (IBD). Preventing or reducing the severity of treatment-induced toxicity is of increasing importance as the number of survivors of cancer treatment increases. Dietary fibre may be an attractive option through the anti-inflammatory action of its fermentation metabolites short chain fatty acids (SCFA) and its beneficial effect on stool frequency and form.

Methods

A systematic review of the efficacy of dietary fibre in the management of IBD was undertaken. The aims were firstly to identify evidence for the manipulation of dietary fibre in this inflammatory condition of the bowel as it was anticipated that little evidence would be available in patients receiving pelvic radiotherapy and secondly to gain insight as to the nutritional interventional approaches employed. A further systematic review was undertaken to identify evidence for the efficacy of dietary fibre manipulation in patients receiving pelvic radiotherapy. A 3-arm randomised controlled trial (RCT) manipulating dietary fibre intake in pelvic radiotherapy patients was subsequently carried out, powered on the difference in the change in Inflammatory Bowel Disease Questionnaire - Bowel subset (IBDQ-B) score between study groups consuming a high fibre, low fibre or habitual dietary fibre intake measured as non-starch polysaccharide (NSP) in g/day. Other measurements included concentration of faecal SCFA at start and end of radiotherapy, daily patient-reported bowel habit using the Bristol Stool Form scale and quality of life assessed using the IBDQ tool.

Results

A total of 4232 original citations were identified in the systematic review of fibre in IBD, of which 23 articles (1296 patients) were included. Evidence for the efficacy of increased dietary fibre on disease outcomes was found in 4/23 RCTs, 3/10 in ulcerative

colitis and 1/1 in pouchitis. Meta-analysis was not possible due to widely differing study designs. The systematic review of fibre during pelvic radiotherapy identified 4188 original citations of which 4 articles (264 patients) were included. Meta-analysis (2 studies) showed increased or modified dietary fibre to be of benefit as a prophylactic against new-onset diarrhoea with a risk ratio of 0.75 (95% CI: 0.56 – 1.01). However, this result was not statistically significant (p=0.06). A total of 166 patients were randomised to the 'Fibre Study' RCT with 159 providing evaluable data of the required 156 patients. A significant difference in the change in IBDQ-B score between baseline and end of radiotherapy was identified between the high fibre and no intervention (control) group of 7.7 points in favour or the high fibre group (p=0.007). A difference in the change in IBDQ-B score of 3.4 points was also found between the low fibre and control group in favour of the low fibre group although this difference was not significant (p=0.535). No significant differences between groups were found in the incidence of loose stool (Bristol Stool type 6/7) or stool frequency although there was a marked increase in the use of anti-diarrhoeal medication by the high fibre group during week 5 of radiotherapy treatment. Mean (sd) NSP consumption of the control, low and high fibre groups at the start of radiotherapy was 13.6 (5.3), 10.2 (3.4) and 17.1 (4.8) g / day and at the end of radiotherapy was 12.2 (5.2), 8.9 (2.9) and 15.7 (5.1) g / day. No significant difference between groups in the concentration of faecal SCFA was found (n=41 paired samples) between start and end of radiotherapy. There was a significant difference in the change in IBDQ quality of life scores between the high fibre and control groups between start and end of radiotherapy in favour of the high fibre group (p=0.010)

Conclusion

Dietary advice to increase fibre during pelvic radiotherapy may protect against bowel symptoms compared to no dietary advice. However, advice to reduce fibre intake may also be of benefit compared to no dietary advice. High and low fibre intakes may have differing, independent benefits in comparison to ad-libitum intake. High fibre intake did not adversely affect stool frequency or type although use of anti-diarrhoeal medication may have masked these effects. The possible placebo effect of specific dietary advice *versus* no dietary advice is intriguing and merits further exploration.

Acknowledgements

The work described in this thesis has been made possible by patients. Without their agreement to participate in clinical research we could not have performed this research. Thank you to all of them.

A whole host of other people have contributed in so many ways. Thanks to my colleagues in the dietetic office in Sutton, to Eva Grace my research colleague, to Amyn Lalji and Kabir Mohammed for making sense of data and to Barbara Benton and Michelle Davies for their analysis of food diaries. My thanks to Dr Helen McNair, Senior Research Radiographer, Royal Marsden NHS Foundation Trust, Sutton for helping me to understand the rudiments of radiotherapy and with whom it has been a pleasure to collaborate.

Thanks also to Tanya Klopper and Lindsey Bottle, Oncology Dietitians at The St Luke's Centre, The Royal Surrey County Hospital, Guildford. Thanks to all collaborating clinical oncologists at both hospital sites for their enthusiasm, advice and support. Special thanks to Dr Jervoise Andreyev (Royal Marsden NHS Foundation Trust), Professor Kevin Whelan (King's College London) and Dr Clare Shaw (Royal Marsden NHS Foundation Trust): Jervoise for employing me in the first place and giving me the wonderful opportunity to work within his research group and for his great insight, support and vision; Kevin for his uncompromising expectation of excellence and energy in driving me forward and Clare, not least for allowing me to occupy a coveted position in the Dietetic Department for so many years but also for her continuing unbiased, thoughtful and sound advice.

I suspect that it may be quite stressful to live with someone undertaking a PhD. Heartfelt thanks to my partner Jennifer for her patience and understanding. Thanks to my mother Jean Wedlake, who long chastised me for being a perpetual student but I hope, will agree with me that on this occasion it was worth it. Finally, to precious Lottie I dedicate this thesis.

Publications related to work conducted in thesis

Wedlake L, Slack N, Andreyev HJ, Whelan K. Fiber in the treatment and maintenance of inflammatory bowel disease: a systematic review of randomized controlled trials. *Inflamm Bowel Dis*. 2014 20(3):576-86

Wedlake LJ, Shaw C, Whelan K. Andreyev HJN. Systematic Review: the efficacy of nutritional interventions to counteract acute gastrointestinal toxicity during therapeutic pelvic radiotherapy. *Aliment Pharmacol Ther*. 2013 37: 1046-56

Glossary of Abbreviations

5-FU	5-Fluorouracil
#	Fraction (of radiotherapy)
ACE	Angiotensin Converting Enzyme
AIDS	Auto Immune Deficiency Syndrome
AJCC	American Joint Committee on Cancer
ANOVA	Analysis of Variance
AOAC	Association of Official Analytical Chemists
AP-1	Activator Protein 1
ASPEN	American Society of Parenteral and Enteral Nutrition
ASTRO	American Society for Therapeutic Radiology and Oncology
ATG	Autophagy (gene)
AUC	Area under the curve
BAPEN	British Society for Parenteral and Enteral Nutrition
BMI	Body Mass Index
BRCA1/2	Genetic mutations
BSC	Bristol Stool Chart (Bristol Stool Form Scale)
BSO	Bilateral Salpingo-Oophrectomy
CAB	Commonwealth Agricultural Bureau
cAMP	cyclic Adenosine Monophosphate
CCNFSDU	Codex Committee on Nutrition and Foods for Special Dietary Purposes
CCR	Committee for Clinical Research
CD	Crohn's Disease
CENTRAL	Cochrane Central Register of Controlled Trials
CFU	Colony Forming Units
CHO	Carbohydrate
CI	Confidence Interval
CINAHL	Cumulative Index to Nursing and Allied Health
Cis	Cancer-*in-situ*

CIN	Carcinoma in Situ
CINC	Cytokine-induced Neutrophil Chemoattractant
COMA	Committee on Medical Aspects of Food
CONSORT	Consolidated Standards of Reporting Trials
COX-1/2	Cyclooxygenase
CQLE	Consequential Late Effects
CRP	C-reactive protein
CT	Chemotherapy
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CTGF	Connective Tissue Growth Factor
CXC	Chemokine
DAI	Disease Activity Indices
DAMP	Damage Associated Molecular Pattern
DARE	Database of Abstracts of Reviews of Effects
DNA	Deoxyribonucleic Acid
DP	Degree of Polymerisation
DRV	Dietary Reference Value
DVH	Dose Volume Histogram
EBRT	External Beam Radiotherapy
ECP	Eosinophilic Cationic Protein
ELISA	Enzyme-Linked ImmunoSorbent Assay
EORTC	European Organisation for Research & Treatment of Cancer
ESPEN	European Society for Nutrition and Metabolic Medicine
ESR	Erythrocyte Sedimentation Rate
ESTRO	European Society for Therapeutic Radiology and Oncology
FAIMS	Field Asymmetric Ion Mobility Spectrometry
FFQ	Food Frequency Questionnaire
FIGO	International Federation of Gynaecology and Obstetrics
FOS	Fructooligosaccharides
GC	Gas Chromatography
GCP	Good Clinical Practice

g/d	grams per day
GP	General Practitioner
GvHD	Graft versus Host Disease
Gy	Gray (Radiotherapy)
HDR	High Dose Rate (Brachytherapy)
HMGB1	High Mobility Group Box 1 proteins
HMG Co-A	Hydroxymethyglutaryl Coenzyme-A
HPV	Human Papilloma Virus
HSP	Heat Shock Protein
IBD	Inflammatory Bowel Disease
IBDQ	Inflammatory Bowel Disease Questionnaire
IBDQ-B	Inflammatory Bowel Disease Questionnaire – Bowel Subset
IBS	Irritable Bowel Syndrome
ICAM	Intracellular Adhesion Molecule
IFN-ɣ	Interferon gamma
Ig	Immunoglobulin
IGD	Institute of Grocery Distribution
IGRT	Image-Guided Radiotherapy
I-κB	Inhibitor of protein Kappa Beta
IL	Interleukin
IMRT	Intensity Modulated Radiotherapy
ISI	Web of Science (formerly International Science Citation Index)
ISOO	International Society of Oral Oncology
KCL	King's College London
KDa	Kilodalton
LCT	Long Chain Triglycerides
Linac	Linear Accelerator
LPS	Lipopolysaccharide
MAPK	Mitogen Activated Protein Kinase
MASCC	Multinational Association of Supportive Care in cancer
MCT	Medium Chain Triglycerides
MFI	Multidimensional Fatigue Index

MHC	Major Histocompatibility Complex
MMP-2, 9	Matrix Metalloproteinases
MPO	Myeloperoxidase
MyD88	Intracellular protein
NCI	National Cancer Institute
NF-κB	Nuclear Factor Kappa Beta
NOD	Nucleotide Oligomerisation Domain
ns	Not Significant (statistical)
NSP	Non-Starch Polysaccharide
OAR	Organs at Risk
ORS	Oral Rehydration Solution
OTU	Operational Taxonomic Unit
p	Probability (statistical)
PAMP	Pathogen Associated Molecular Pattern
PDGF	Platelet Derived Growth Factor
PICOS	Population, Intervention, Comparisons, Outcomes, Study Design
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PRR	Pattern Recognition Receptor
PTV	Planned Target Volume
QoL	Quality of Life
RCT	Randomised Controlled Trial
RhoK	Rho Kinase ('ROCK')
RMH	Royal Marsden Hospital
ROS	Reactive Oxygen Species
RR	Relative Risk or Risk Ratio
RS	Resistant Starch
RSCH	Royal Surrey County Hospital
RT	Radiotherapy
RTOG	Radiation Therapy Oncology Group
SCFA	Short-Chain Fatty Acids
sd	Standard Deviation

SI	International System of Units
SIBO	Small Intestinal Bacterial Overgrowth
SNP	Single Nucleotide Polymorphisms
TAH	Total Abdominal Hysterectomy
TGF-beta	Transforming Growth Factor-beta
Th	Helper T cell (immunology)
Tis	Tumour-*in-situ*
TLR	Toll-like Receptor
TM	Thrombomodulin
TNF-α	Tumour Necrosis Factor alpha
TNM	Tumour Node Metastases (cancer staging)
Treg	Regulatory T cell (immunology)
UC	Ulcerative Colitis
UK	United Kingdom
UKRO	UK Radiation Oncology group
US	United States (of America)
VAS	Visual Analogue Scale
VAIN	Vaginal Intraepithelial Neoplasia
VCAM	Vascular Adhesion Molecule
VIN	Vulval Intraepithelial Neoplasia
WHO	World Health Organisation

Table of Contents

Index of Tables

Index of Figures

CHAPTER 1: Introduction

1.1 Background to clinical setting

Cancer is a vast medical problem and a major cause of mortality both in the UK and the rest of the Western world[1]. Current estimates suggest that worldwide, the number of cancer cases is rising by about 1.5% per annum[1]. In the UK, this figure is likely to increase as the percentage of the population aged over 65 years rises from 16% in 2004 to an estimated 23% by 2030.

The term pelvic cancer refers to cancers that arise from anatomical sites within the pelvis, defined as the region extending from lumbar vertebra L4 to the anal verge[2]. Pelvic cancer includes tumours of a gynaecological, urological or lower gastrointestinal origin. In the UK in 2011 of the 331,487 new cancer diagnoses 35% (116,294) were of pelvic origin (**Table 1.1**)[3].

Table 1.1 New Pelvic Cancer Diagnoses in the United Kingdom: 2011

Cancer site	Incidence
Urological	**Total: 52,135**
Bladder	10,399
Prostate	41,736
Gynaecological	**Total: 20,114**
Uterine	8,475
Ovary	7,116
Cervix	3,064
Vulva	1,203
Vagina	256
Lower Gastrointestinal	**Total: 44,045**
Colon	27,355
Rectum and recto-sigmoid	14,226
Small Intestine	1,289
Anal	1,175
TOTAL (All pelvic diagnoses): 116,294	

Radiotherapy remains the most important non-surgical treatment in the management of cancer[4] and is widely employed in the treatment of pelvic cancers. A recent report

from the UK Royal College of Radiographers assessing the contribution of different modalities to cancer cure rates, estimated that 'of those cured, 49% are cured by surgery, 40% by radiotherapy and 11% by chemotherapy'[5].

Estimating the number of patients treated with curative, long-course (radical) radiotherapy in the UK is complicated by the fragmentation of UK cancer registries and the lack of uniformity in data reported. The most recent quantitatively-based estimate reported that 12,000 patients received long-course pelvic radiotherapy annually[6]. However, this figure, derived in 2003 is likely to have risen in the last decade.

The proportion of patients with new pelvic cancer diagnoses in whom radiotherapy (of palliative or curative intent) is clinically indicated is 45%[7]. Assuming that 30 to 40% of these patients will require long-course treatment with curative (rather than short course palliative) intent, with reference to **Table 1.1**, the number of patients receiving long-course pelvic radiotherapy in 2011 in the UK is estimated to be between 15,699 and 20,929. One recent publication estimates the figure to be 17,000 patients per annum[8].

However, despite major advances in the planning and delivery of radiotherapy, the tolerance of normal tissues within the radiotherapy treatment field remains dose-limiting. For pelvic tumours, treatment-induced gastrointestinal toxicity as an unwanted side-effect of treatment causes acute and chronic morbidity of varying severity.

As the number of long term survivors of pelvic cancer continues to grow, estimated to be in excess of 3 million in the US in 2013, strategies to limit its damaging side-effects are acknowledged as becoming increasingly important[9]. It is in this clinical setting and against this backdrop that the research described in this thesis has been conducted.

1.2 Therapeutic pelvic radiotherapy

1.2.1 Radiotherapy: an introduction

The delivery of therapeutic, high voltage, ionising radiation with the explicit intention of destroying cancerous cells (radiotherapy) remains a critical component of cancer treatment. Over 50% of patients will receive this form of treatment at some time during the management of their malignant disease[4] either alone or in combination with surgery and/or chemotherapy. The most common treatment modality is external beam radiotherapy (EBRT) which is delivered in the form of very high energy, collimated and flattened x-ray beams of 4-25 Mega electron volts (MeV) generated by a linear accelerator or 'Linac'.

Designed to be skin-sparing, these mega-voltage beams penetrate the human body to predetermined depths to destroy cancerous cells through the process of ionisation (i.e. the displacement of an electron from its orbital path and the creation of an unstable or 'ionised' atom and free electron) with ensuing particle chain reactions and free radical mediated damage. The nuclear DNA of cancer cells is the primary target of this planned radiobiological destruction. The effects may be immediate cellular ablation or, often quantitatively more significant, latent but permanent damage which is expressed when the cells attempt to divide.

Total prescribed radiotherapy dose is defined in Gray (Gy) the SI unit of absorbed radiation dose. The prescribed radiation dose, which for long-course treatments is typically 45 to 54 Gray, is divided into a series of equal daily fractions. Fractionation is intended to exploit the differential in the cytotoxic effect of ionising radiation on cancerous *versus* normal tissue, reparative processes being generally greater in normal tissues through which the radiation beams inevitably pass to reach their target.

For any given tumour, the greater the reparative powers of normal cells compared to tumour, the wider the therapeutic window and thus the increased certainty of tumour control with minimised damage to normal cells.

Dose per fraction for treatments relevant to the thesis is generally 1.8 Gray per fraction and thus a prescription dose of 45 Gray delivered at a rate of 1.8 Gray / fraction would require the patient to attend for 25 treatments over an elapsed time of at least five weeks, assuming a Monday to Friday treatment schedule.

During pelvic radiotherapy the normal tissues or organs that may lie within the (pelvic) radiotherapy field are at risk of radiation-induced damage. They include the distal portion of the small bowel, the terminal ileum, the caecum, the large bowel including the ascending, mid-transverse, sigmoid colon and rectum. In wide pelvic fields, which may encompass pelvic lymph nodes, it is not uncommon for loops of the small bowel or transverse colon to dip down into the field thus also receiving radiation dose. Treatment margins which allow for systematic and random treatment errors in patient set-up or positioning add to the overall treatment volume.

Organ motion, which is technically difficult to control may further contribute to the dose received by normal tissues and may vary both intra- and inter-fractionally (i.e. during the delivery of individual fractions and between fractions). Daily treatment is usually based on the acquisition of a single computed tomography planning scan in which transverse slices through the pelvis are acquired at 5 or 7 mm intervals and upon which both tumour volume and organs at risk are delineated. Typically, but not in all instances, a dose volume histogram is produced which constitutes a composite 2-dimensional graphical representation of the total dose to be delivered to the tumour and the dose that will be received by all adjacent structures.

Brachytherapy describes the use of small, sealed radioactive sources placed close to the tumour delivering a high dose to a small target volume[10]. Brachytherapy limits the dose to normal tissue as dose falls quickly with increasing distance from the radioactive source. The use of High Dose Rate (HDR) systems is now widespread in the UK and uses radioisotopes of very high specific activity such as cobalt (60-Co) and Iridium (192-Ir) which have important practical advantages over Low Dose Rate systems[10]. After loading delivery techniques allow remote handling and accurate placement and verification of applicators. Treatment takes place in a shielded room.

HDR intracavity brachytherapy is commonly used as adjuvant treatment in cervical and endometrial cancers[11]. Cervical applicators are usually placed under anaesthetic as dilation of the cervical canal is required and treatment delivery takes place over several days with the patient remaining in hospital. In endometrial tumours, a plastic tube is inserted into the vagina to carry the afterloading catheter and treatments delivered over two to three daily sessions, typically each delivering 4.0 Gy at a distance of 5 mm from the applicator surface[10].

1.2.2 Treatment induced gastrointestinal toxicity

In recent years, the increasing use of computer technology and the involvement of highly skilled medical physicists have enabled the radiotherapy planning process to become increasingly sophisticated. Further, the introduction of advanced radiotherapy delivery techniques including intensity modulated radiotherapy (IMRT), image-guided radiotherapy (IGRT) and Cyberknife techniques has enabled radiographers to deliver daily treatment fractions with millimetre precision.

Despite these advances, normal tissue tolerance remains the limiting factor in escalating tumour dose. Organ motion continues to challenge the ability of radiotherapists (without daily image guidance) to replicate initial CT planning geometry at each treatment fraction. To date, patient-centric approaches to standardise organ motion have so far met with only limited success[12]. Unlike 'adverse events' which can be defined quite specifically in the context of new medical treatments or procedures, treatment-induced radiation toxicity was, until recently an ill-defined concept.

The term toxicity refers to unwanted radiation-induced damage or injury to normal tissues as distinct from planned destruction of malignant cells. In 2010 a new unified definition of pelvic radiation disease was proposed as 'transient or longer term problems ranging from mild to very severe, arising in non-cancerous tissues resulting from radiotherapy treatment to a tumour of pelvic origin'[13]. Comprehensive guidelines

for the diagnosis and management of symptoms resulting from cancer treatment (i.e. radiotherapy and/or chemotherapy and/or surgery) were published soon afterwards[14].

The definition of pelvic radiation disease and associated guidelines will legitimise radiation induced toxicity although recent evidence suggests that the provision of clinical services for patients may remain sub-optimal for some time. A survey of 314 clinical oncologists in 2011 reported that although 76% screened for gastrointestinal problems following pelvic radiotherapy, less than 10% referred patients to a gastroenterologist or gastrointestinal surgeon[8].

Failure or reluctance to refer patients to specialist services probably reflects the fact that very few specialist centres exist to treat these patients. The low response rate of gastroenterologists (20%) to a more recent survey in which they were asked to give their opinion on the provision of such services indicates that few even regard it as a significant problem[15].

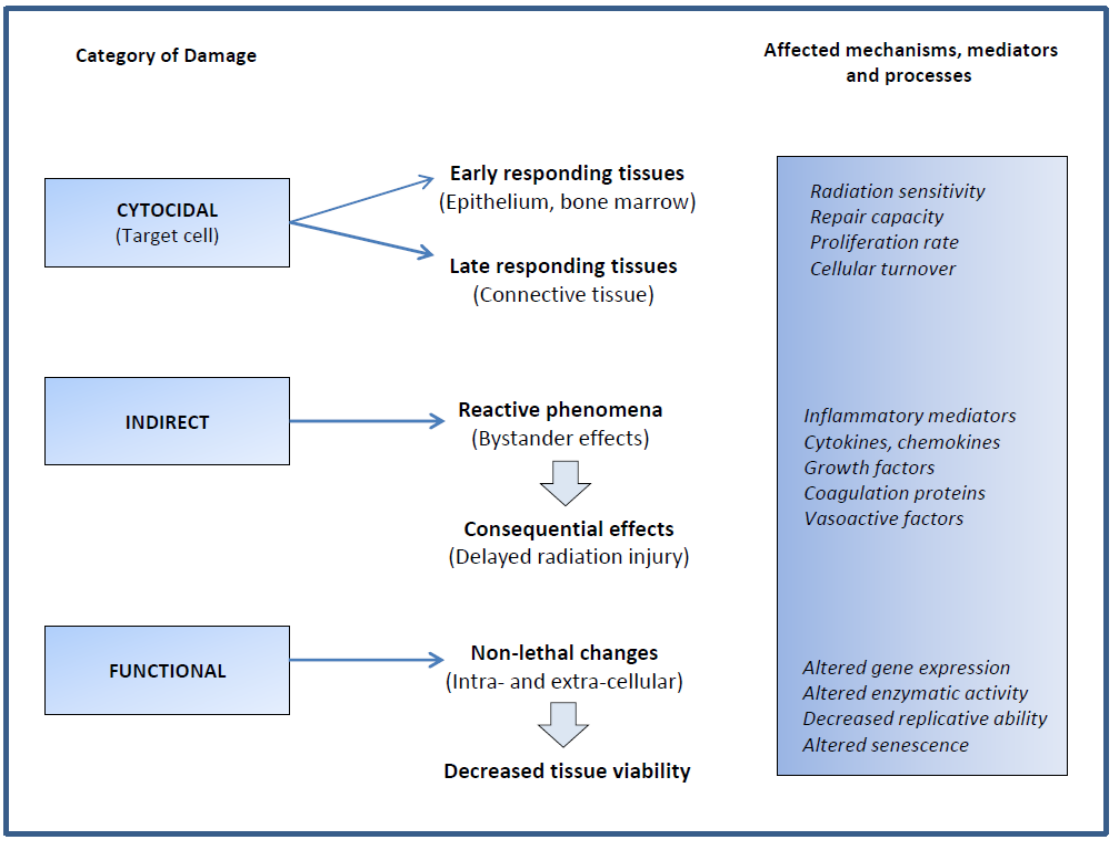
1.2.2.1 Scope and nature of toxicity

Radiation-induced toxicity in normal tissues was initially described in terms of the target-cell hypothesis[16]. Under this model the effect of ionising radiation on non-cancerous (normal) tissues and organs was thought to be a direct consequence of cell killing, resulting in the depopulation of crucial cell lines and subsequent functional deficiency[17]. This radiobiological model prevailed until the mid-1990s when a more holistic view of damage was proposed to take account of the fact that quantitative damage to specific cellular lineages alone could not explain the range of late (or chronic) effects emerging months to years after treatment[16].

Radiation-induced toxicity has since been described as a radio-therapeutic injury in which tissues within the irradiated volume are responding to insult through normal wound healing mechanisms whilst at the same time undergoing a series of transient or permanent alterations to cellular and extracellular components[18]. Reparative processes are unable to resolve due to repeated fractionated insults with resulting ongoing damage to organised tissues.

In 2001, a new classification of radiation toxicity into cytocidal, indirect and functional effects was proposed. Acute toxicity was recognised as being characterised by a mucosal inflammatory processes, whilst in the chronic or late toxicity, submucosal, ischaemic and fibrotic mechanisms predominate (**Figure 1.1**)[16].

Figure 1.1 Proposed categorisation of normal tissue radiation injury



Source: Figure derived by author based on information in Denham[16]

Many studies in the last decade have augmented our understanding of the molecular mechanisms and mediators of damage depicted in the above model (**Section 1.3.3).** Further, emerging data on the role of the gut microbiota and immune systems point to the critical role they play in orchestrating inflammatory mechanisms.

Mechanistic, cellular damage in the gastrointestinal tract leads to organ dysfunction. Disruption to normal secretory and absorptive functions includes malabsorption of disaccharides, bile acid malabsorption and small intestinal bacterial overgrowth due to

disruption of normal gastrointestinal motility and normally benign gastrointestinal secretions (e.g. bile acids and pancreatic enzymes) potentiate damage to an already inflamed mucosa.

1.2.2.2 Definition and prevalence of acute and late toxicity

Radiation-induced toxicity has historically been divided into acute and late reactions or 'effects'[19]. Acute reactions are defined as those occurring during treatment or in the three months immediately following treatment and may lead to symptoms. Research investigating time patterns of endoscopic and histological change in the acute setting has shown that symptoms tend to start during the second week of treatment (when histological damage is at a maximum) and peak towards the end of treatment (week 4 to 5) when histological changes are stabilising or improving,[20 21].

These acute changes may resolve 9 - 10 weeks post treatment[20 22 23]. However objective, prospective, histological data on toxicity is rare. Assessment of acute toxicity is addressed in more detail below but generally relies on the measurement of symptoms. However, robust prospective data on the nature and severity of gastrointestinal symptoms and impact on quality of life in large cohorts are lacking.

Attempts to correlate changes in symptom scores with histological findings or biomarkers have failed to yield definitive evidence of an association[22 24]. Accurate assessment of the prevalence of acute toxicity, where prevalence is defined as 'the proportion of individuals in a population who have the disease at a specific instant[25]' is also limited by the blunt or varied nature of scoring tools in current use.

Table 1.2 shows the prevalence of gastrointestinal symptoms in a recent cohort of 107 patients receiving pelvic radiotherapy, comprising 36% urological, 28% colorectal and 36% gynaecological patients[6]. The reported prevalence of the impact of acute gastrointestinal symptoms on lifestyle activities in the same cohort is shown in **Table 1.3**[6].

Table 1.2 Prevalence of acute gastrointestinal symptoms during pelvic radiotherapy

Symptoms	Prevalence (%)
Gastrointestinal symptoms:	
Change in bowel habit	94
Loose stool	80
Frequency	74
Flatulence	65
Urgency	39
Faecal incontinence	37
Use of anti-diarrhoeal medication	40

Source: Khalid[6]

Table 1.3 Prevalence of social / lifestyle effects during pelvic radiotherapy

Impact of symptoms on lifestyle	Prevalence (%)
Lifestyle activities	
'Unable to do what you want because of your bowels'	40
'Cancelled an engagement because of your bowels'	20
'Not done leisure or sport because of your bowels'	27
'Not gone somewhere because there is no lavatory nearby'	30
'Felt limited in sexual activity because of your bowels'	14

Source: Khalid[6]

Frequently patients report more than one symptom[26] and frequently one symptom may result from multiple changes or damage to different parts of the gastrointestinal tract. Diarrhoea, for example, can result from one of thirteen different physiological mechanisms[21]. Small intestinal bacterial overgrowth with symptoms of bloating and abdominal discomfort occurs in 26% of patients during pelvic radiotherapy[27]. Bile acid malabsorption and new-onset lactose intolerance, both of which result in diarrhoea, is reported to occur in up to 50% of patients during treatment[21].

Late reactions may occur months or years after treatment ranging in severity from mild and treatable to irreversible, severe or fatal. Serious and life-threatening changes including transfusion-dependent bleeding, fistula formation and bowel obstruction have been reported in 4 – 10% of patients five to ten years after treatment[28 29] and in 15 – 20% of patients twenty years or more after pelvic radiotherapy[30].

Table 1.4 summarises the range and frequencies of patient-reported gastrointestinal symptoms at least three months after pelvic radiotherapy for gynaecological and colorectal or anal cancer[21]. Much of this data is derived from retrospective cohorts.

Table 1.4 Frequency of reported gastrointestinal symptoms after pelvic radiotherapy

Symptoms	**Gynaecological cancer** Reported frequency (%)	**Rectal or anal cancer** Reported frequency (%)
Rectal bleeding	23 – 26%	23 – 25%
Bloating	32 - 45%	13 – 32%
Change in bowel habit	75 – 89%	38 – 93%
Constipation	21%	No data available
Diarrhoea (loose or soft stool)	52%	5 – 60%
Faecal incontinence	25 – 47%	7 – 60%
Increased frequency (of defaecation)	56%	14 – 59%
Excessive flatulence	23 – 50%	38 – 55%
Pain (abdominal, rectal, perineal)	34 – 52%	13 – 27%
Tenesmus	14 – 31%	13 – 36%
Urgency (of defaecation)	48 – 53%	14 – 78%

Source: Adapted from Andreyev[21]

The lack of prospective, long-term, post-treatment, outcome data and use of blunt symptom scoring tools insensitive to the range of late reactions that can occur may bias the outcomes reported[21] and complicates the synthesis of data. Further, there is no consensus regarding time since treatment for onset of late effects. A recent survey

of clinical oncologists (190 responders) reported that at least 24% of patients could be expected to present with gastrointestinal symptoms one year after treatment[8]. **Table 1.5** illustrates the range of different definitions used by different authors.

Table 1.5 Time-points for assessing late GI toxicity after pelvic radiotherapy

Author (year)	Time points / definitions for defining onset of late effects
Schultheiss (1997)[31]	A median of 13.7 months found as the latency period for the emergence of late Grade 2 gastrointestinal morbidity.
Wang (1998)[32]	18 months post treatment found to be the time of peak prevalence of radiation proctitis. 47% of patients experiencing severe diarrhoea during treatment were found to be symptomatic after 12 months.
Denham (1999)[33]	The 'vast majority' of symptoms associated with the chronic proctitic syndrome found to develop in the first 24 months following treatment.
Weiss (1999)[34]	Half of all complications are diagnosed within approximately the first year after treatment
Jereczek-Fossa (2002)[35]	Late reactions defined as those occurring after 90 days from completion of radiotherapy. Late bowel reactions occur a median of 11 months after the completion of radiotherapy.
O'Brien (2002)[36]	Patients followed-up every 3 and then 6 months for 63 months.
Peters (2005)[37]	Late toxicity scored from 120 days after start of radiotherapy treatment.
Vargas (2005)[38]	Grade 2 gastrointestinal toxicity found to be present in 10.3% of patients at 1.1 years.
Heemsbergen (2006)[39]	Patients followed-up every 3 months for the first year after treatment and then every 6 months.
Zelefsky (2008)[40]	Median time to development of late gastrointestinal toxicity found to be 17 months (range: 4 – 102 months)

Source: Author's data (unpublished)

1.2.3 Consequential late effects (CQLE)

The term 'consequential late effects' (CQLE) has been used to describe pathophysiological mechanisms that occur secondary to acute radiation injury and contribute to injury that manifests itself sometime after apparent healing of the early injury[16]. However, it is now recognised that cytocidal, indirect and functional effects (**Figure 1.1**) all contribute to late, chronic or 'delayed' radiation injury and that it is somewhat artificial to attempt to separate toxicity into acute and late effects[16].

It is now recognised that models such as Normal Tissue Complications Probability modelling and outcome predictions based on alpha/beta ratios, which attempt to classify organs as 'early' or 'late' responding in terms of their cytotoxic cellular response to fractionated radiotherapy, fall far short of describing the long-term response of complex multi-cellular tissues to radiation[16 39 41 42].

It is appreciated that increasing radiotherapy dose leads to accumulating tissue dose and thus incremental damage or toxicity. Toxicity in the acute setting is characterised by an inflammatory response in the gastrointestinal mucosa, which leads to microvasculature damage and resulting ischaemia and fibrosis in the late setting. These tissue responses to radiation cause symptoms because they compromise normal gastrointestinal tract physiology. However, the relationship between accumulating dose and resulting toxicity is not straightforward.

Long-term outcomes in patients receiving the same radiotherapy dose, with similar volumes of normal organs at risk, can be very different. The point is well illustrated by a recent retrospective analysis of 388 patients receiving radical radiotherapy for prostate cancer[43]. Stringent rectal constraints (i.e. the maximum volume of rectum to receive a specified radiotherapy dose) were applied to planning data to reveal the number of patients who met or did not meet the specified dose constraints and compared to the same patients' self-reported toxicity data.

In theory, patients who failed no dose constraints could be expected to experience minimal rectal toxicity. However, the analysis showed that even in patients who failed no constraints, 35% still experienced grade 2 (moderate/severe) rectal toxicity including rectal bleeding and urgency[43].

Further, a number of authors have shown that the severity of toxicity experienced acutely predicts for the severity of late effects [31-36] [38-40] [44] [45] and several have highlighted that this association is independent of dose received[32] [39]. However, one complication in predicting those patients at most risk of late toxicity, on the basis of the severity of the acute reaction, is the lack of consistency in the measurement of acute symptoms as a surrogate for toxicity. Analyses using approaches such as Area under the Curve (AUC) and Integrated Longitudinal Toxicity have shown that moderate but sustained toxicity, rather than a single severe peak in symptoms, may predict more strongly for late toxicity[46] [47].

The importance of the contribution of the as yet incompletely defined (non-treatment related) factors that influence both acute and late outcomes is that they provide an opportunity for manipulation for patient benefit[9]. Simple and cost-effective interventions such as anti-inflammatory nutritional strategies may help to limit the extent of acute and thus late damage. Low Body Mass Index (BMI) and cessation of smoking, both of which can be addressed and treated, also predict for greater toxicity[46].

Other factors which may influence outcomes include genetics, gastrointestinal co-morbidities (e.g. history of Inflammatory Bowel Disease) and the nature of the host's gut bacteria or microbiota[48] [49]. Our group has also recently shown that the use of certain medications including statins (HMG Co-A Reductase inhibitors) and Angiotensin Converting Enzyme (ACE) inhibitors may be protective for non-cancerous tissue [50].

1.2.4 Toxicity assessment and measurement

1.2.4.1 Toxicity versus symptoms

The objective assessment and measurement of treatment-induced toxicity is problematic. Symptom scoring is a poor surrogate of toxicity giving only limited or no insight as to underlying pathophysiological mechanisms. Reliable biomarkers of gastrointestinal damage would be a significant advantage in the radiotherapy setting but none of a number of the possible candidate markers has yet proved sufficiently reliable to be recommended for routine clinical use.

At least ten small studies have been conducted investigating the potential efficacy of different blood and faecal markers in the pelvic radiotherapy setting but the available data is sparse and lacking in large homogeneous cohorts. Meta-analysis is hampered by the diversity of approach and differing outcomes employed.

In the absence of a gold standard biomarker of toxicity there remains a reliance on scoring tools to assess treatment-induced toxicity. Some of these tools focus exclusively on patient reported symptoms which in terms of importance or severity may differ markedly from the views and interpretation of the responsible clinician[51].

Also, as our research group and others have shown, the correlation between symptoms and objective assessment of treatment-induced toxicity, at least with the biomarkers evaluated to date, remains poor[22-24]. Truly objective data regarding the measurement of treatment-induced gastrointestinal damage (e.g. histological scoring based on acquisition of data from biopsied gut) is rarely available and requires invasive procedures to acquire. Histological damage of the gastrointestinal mucosa in both IBD and radiation-induced gastrointestinal toxicity is in any case, poorly associated with symptoms[20 22 23].

Ideally, the term toxicity should be reserved to describe the unintended effects of treatment (in the case of this thesis, radiation-induced damage to non-cancerous gastrointestinal tissue) and must be assessed (or quantified) in an objective manner to

give insight as to possible future risk related to scope and severity of damage. Clearly, whilst symptoms may reflect underlying damage and loss of function they do not equate to toxicity.

A recent communication to the author from a clinical gastroenterologist dealing with both acute and late effects of pelvic radiotherapy illustrates the point: "….diarrhoea on day 20 (of treatment) could be due to an entero-enteric fistula (terrible toxicity), new onset, transient, lactose intolerance due to brush border enzyme dysfunction (maybe less important with limited long-term sequelae), new onset bile acid malabsorption (of unpredictable long-term importance) *OR* a community acquired infection, suspect food item on day 19 (of treatment), ….. etc, etc." [52].

The evolution of different scoring tools for the assessment of pelvic radiation-induced gastrointestinal toxicity is described in more detail below (**Section 1.3.5**). Whilst a number of important improvements have been made to these tools over the years, the choice of instrument is limited.

Many studies employ a range of tools and although the collection of data to complete multiple scales may appear excessive and possibly unwarranted, it enables useful comparison and should facilitate their future refinement[51].

1.2.4.2 Biomarkers of toxicity

A biomarker is a biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease[53]. No one 'gold standard' marker for gastrointestinal damage resulting from therapeutic pelvic irradiation exists.

Since 2011, ten studies have investigated the use of various plasma or faecal biomarkers of gastrointestinal toxicity resulting from pelvic radiotherapy (**Table 1.6**).

Table 1.6 Studies investigating biomarkers of toxicity during pelvic radiotherapy

Sample: / ***Marker:***	**Plasma**			**Stool**	
	Citrulline	ECP	CRP	Calprotectin	Lactoferrin
Author year					
Onal 2011[54]	√				
Jakobsson 2010[55]	√		√		
Hille 2009[56]				√	√
Wedlake 2008[24]	√	√	√	√	
Larsen 2007[23]				√	√
Bowen 2005[57]		√			
Lutgens 2004[58]	√				
Larsen 2004[59]				√	√
Koc 2003[60]			√		
Cengiz 2001[61]			√		
TOTAL STUDIES:	**4**	**2**	**4**	**4**	**3**

KEY: ECP: eosinophyllic cationic protein, CRP: C-Reactive Protein

Two narrative reviews have also been published[53 62] but no systematic reviews or meta-analyses. The need for an objective measure of damage is recognised and will enable a better examination of the relationship between toxicity and symptoms[42 53].

1.2.4.3 Plasma Biomarkers

The amino acid citrulline is the end-product of glutamine metabolism in small intestinal enterocytes. These cells lack the cytosolic enzymes required to convert citrulline to arginine and this, coupled with the fact that citrulline is not metabolised by the liver, means that plasma citrulline reflects small bowel enterocyte mass and thus functional capability[63].

In coeliac disease, citrulline concentrations of ≤ 10 µmol/l (equating to 25% of the mean normal value) are indicative of severe and extensive villous atrophy and values ≤ 20 µmol/l indicative of severe atrophy[64] Four prospective cohort studies have explored the citrulline as a possible biomarker of toxicity during pelvic radiotherapy[24 54 55 58]. In

all four studies levels fell significantly compared to baseline after 3 and 5 weeks of radiotherapy However, in no studies did concentrations reach levels associated with severe villous atrophy (**Table 1.7**)[64].

Table 1.7 Citrulline levels in prospective cohorts of pelvic radiotherapy patients

Author	n	Baseline (µmol/l) Mean (sd) or Average (range)	3 weeks (µmol/l) Mean (sd)	5 weeks (µmol/l) Mean (sd)
Wedlake[24]	50	28.1 (7.6)		25.9 (9.2)*
Lutgens[58]	23	30.9 (19.1 – 52.9)	23.6 (2.4)*	
Jakobsson[55]	29	41.0 (11.0)	28.0 (9.6)*	26.0 (9.8)*
Onal[54]	53	38.0 (10.1)	27.4 (5.9)*	

KEY: * significant difference (p<0.005) compared to baseline (start of radiotherapy)

In the earliest study, which assessed citrulline concentrations weekly during treatment, lowest mean citrulline concentrations were observed at 3 weeks of treatment, co-incident with a peak in the number of patients with maximum toxicity (RTOG=2) assessed using the Radiation Therapy Oncology Group scoring tool and fewest number of patients with absence of symptoms ('% zero score').

However, a significant correlation between toxicity, measured using the RTOG tool, and citrulline levels was found only at week 4 (p=0.007) and week 6 (p=0.027)[58]. Whilst the total time during treatment with absence of symptoms (% zero score) correlated with the overall change in citrulline concentration (p=0.002), no relationship was observed between maximum toxicity (RTOG 2) and citrulline concentration[58].

Further, citrulline concentrations fell in 17/23 patients (mean decrease: 43%) during treatment but rose in 5/23 (mean increase: 38%) and remained unchanged in one patient. Despite this, a significant decrease in citrulline concentration was observed as a function of increasing radiation dose and of increasing volume of small bowel treated. The authors noted the lack of correlation between maximal toxicity and

citrulline concentration and remarked that several pathophysiological mechanisms, in addition to loss of small intestinal mucosal mass, contribute to clinical symptoms. They also acknowledged the difficulties of correlating subjective measures of toxicity (e.g. RTOG score) with objective endpoints of toxicity[58].

Our research group, using a potentially more sensitive tool for the identification of gastrointestinal symptoms, the Inflammatory Bowel Disease Questionnaire-Bowel subset (IBDQ-B), found no correlation between fall in citrulline concentration and IBDQ-B score after 5 weeks of treatment[24].

Two further studies have been conducted. One, recruited women with uterine or anal cancers and explored the link between fatigue, measured using the Multidimensional Fatigue Inventory (MFI)-20 general fatigue subscale (range of scores attainable: 4 – 20 with higher scores indicating worse fatigue) and epithelial atrophy as evidenced by change in citrulline concentration[55]. The association between the intensity and frequency of radiotherapy-induced diarrhea, assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and the Common Terminology Criteria for Adverse Events (CTCAE) v.3 respectively, and plasma citrulline concentration was also examined[55].

A significant correlation between MFI-20 and citrulline concentration was observed at three but not five weeks (p<0.05) although only five patients had values of <20 μmol/l at the three week time-point and the majority of patients displaying values of between 20 – 30 μmol/l (13/27 patients) and >30 μmol/l (10/27 patients) with MFI-20 scores of >12 or <12 evenly split (i.e. showing no association) between these two concentrations. No correlation between the severity or frequency of treatment-induced diarrhoea and citrulline was found at 3 or 5 weeks[55].

The most recent study evaluated the feasibility of plasma citrulline levels in predicting toxicity in 53 patients receiving radiotherapy for prostate or endometrial cancer[54]. Mean citrulline concentration was significantly reduced at week three and at the end of treatment (**Table 1.12**) compared to baseline values (p<0.0001 for comparison of

both time-points with baseline). In line with previous findings[58], citrulline concentrations fell during treatment in 43/53 patients but rose in 9/53 and were unchanged in one patient. Increased toxicity, measured weekly using the RTOG tool, was significantly correlated with reduced citrulline concentration (p<0.0001) at week 3 and at the end of treatment. However, a 7% change (fall) in citrulline concentration was also noted at week 3 despite patients reporting absence of toxicity (RTOG=0)[54].

Citrulline is a marker of enterocyte mass rather than inflammation. This, coupled with the heterogeneous cohorts used in these four studies, with differing volume of small bowel in receipt of radiation dose may have contributed to these equivocal results.

C-reactive protein (CRP) is an acute phase protein with systemic as opposed to gastrointestinal-specific response. Modest (<10mg/l) but significant rises (p<0.001) in CRP between start and end of radiotherapy in mixed pelvic cohorts have been reported of 1.4 (0.21-9.8) to 2.7g/l (0.12-32.2)[61], 0.70 (±0.12) to 2.74g/l (±0.61)[60], and 3.0 (±8.1) to 14.0 g/l (±25)[55]. However, two of these studies reported no correlation between change in CRP levels and toxicity assessed using the RTOG and EORTC QLQ-C30[55 61].

A third study did not investigate toxicity and only 9 of the 52 recruited patients had pelvic malignancy[60]. Our group reported no significant increase in CRP in 59 patients between start and following 4/5 weeks of radiotherapy[24]. CRP reflects a systemic reponse and is not specific for intestinal injury and change in levels which do rise above 10 g/l are of questionable clinical significance[62].

Eosinophilic cationic protein (ECP) which is released from activated eosinophils has been investigated in two cohorts receiving pelvic irradiation. Although one observational pilot study in 15 patients reported a significant rise in ECP (p=0.02) after 4 weeks of pelvic radiotherapy there was no correlation between the rise in ECP and toxicity assessed using the Common Toxicity Criteria (CTC) v.2[57]. In a later study, our group showed no significant increase in ECP in a mixed pelvic malignancy cohort of 59 patients between start and following 4/5 weeks of radiotherapy[24].

1.2.4.4 Faecal biomarkers

Calprotectin is a 36-kDa calcium binding protein and member of the S100 protein family. It accounts for approximately 60% of the total soluble proteins found in human neutrophils and is released when neutrophils become activated as a direct consequence of underlying organ pathology with increased levels in plasma, urine or faeces[53]. Calprotectin is acknowledged as a biomarker of inflammation in inflammatory bowel disease (IBD) and has been used to differentiate patients with Crohn's disease from those with Irritable Bowel Syndrome (IBS) or non-diseased individuals[65]. Levels of >50 μg/g are considered borderline abnormal and those >100 μg/g strongly positive[65] (**Table 1.8**).

Four studies have examined the potential value of faecal calprotectin as a biomarker of gastrointestinal inflammation during pelvic radiotherapy[23 24 56 59]. However one of these studies aimed to correlate acute and late toxicity and refers to acute data which is only available in a non-English publication (author not contacted) and thus is not discussed further[56]. The results of the remaining studies are equivocal and comparison is hampered by the use of different measurement units. **Table 1.8** compares the results of a study by our group with data from other patient groups[24].

Table 1.8 Calprotectin in pelvic radiotherapy patients and other patient groups

Author	**n**	**Baseline (μg/g) Mean (sd)**	**3 weeks (g/g) Mean (sd)**	**5 weeks (μg/g) Mean (sd)**
Wedlake[24]	59	35.7 (103)		62.9 (121)*
Costa[65] Comparator groups:		Median value and (95% confidence interval)		
Gastrointestinal cancers	26	105 μg/g (0 – 272 μg/g)		
Crohn's Disease	49	231 μg/g (110 – 353 μg/g)		
Ulcerative Colitis	82	167 μg/g (59 – 276 μg/g)		
Healthy subjects	34	11 μg/g (3 – 18 μg/g)		

KEY: * significant difference (p<0.01) compared to baseline (start of radiotherapy)

The results of our group are in line with expectations, including a rise in levels of f. calprotectin after 5 weeks of pelvic radiotherapy with values beyond the threshold considered normal for healthy subjects. However, no correlation was seen between the change in f. calprotectin and clinical symptoms assessed using the IBDQ-B tool (p=0.304)[24].

In a further two studies[23 59], although a significant difference in faecal calprotectin levels between baseline and end-of-radiotherapy (receipt of 60 Gy) was reported (p=0.0005) in one study, in a later study, by the same group, no difference in faecal calprotectin levels between baseline and 6 weeks of radiotherapy treatment was found. Both studies were small, recruiting fifteen[59] and twenty[23] patients with prostate cancer. The possible association between change in faecal calprotectin and toxicity was not explored in the earlier of these studies[59] and in the later one, lack of a significant difference in faecal calprotectin levels precluded correlational analysis[23].

It is possible that neutropenia induced by chemotherapy agents given simultaneously with radiotherapy, may contribute to low levels of granulocytic neutrophils in the bowel resulting in low levels of this biomarker in faeces[53].

The use of an alternative faecal marker, faecal lactoferrin has been examined in two studies[23 59]. Rising lactoferrin concentrations are indicative of disease flares or relapse in IBD[53]. Both studies, reported that concentrations of faecal lactoferrin (mg/kg) rose significantly during radiotherapy, although in the earlier study, the possible association between a rise in the concentration of faecal lactoferrin and clinical symptoms was not explored[59]. In the later study, there was no significant correlation between lactoferrin in stool and symptom scores measured using a bespoke Total Symptom Score index assessing stool characteristics, pain, flatulence, bloating and nausea[23].

In summary, no one reliable biomarker of damage to the gastrointestinal tract during pelvic radiotherapy has been found and it is possible that a combination of markers, measured at specific time-points will yield more promising results. The lack of correlation between change in biomarker and change in symptom score is frustrating

and hampered by the number of different toxicity scoring tools in use of widely varying sensitivity. Some progress has been made with respect to the identification of markers of fibrotic change in the acute setting which may have relevance to chronic change although none of these are in routine clinical use.[66] It seems that the convenience and non-invasive nature of symptom scoring tools means that they will continue to be used routinely in clinical practice to indicate individual patient's tolerance to treatment for some time to come.

1.2.5 Symptom scoring tools: acute radiotherapy setting

1.2.5.1 The development of radiation toxicity scoring tools

The Radiation Therapy Oncology Group was formed in 1971 and their well-established scoring tool, the Radiation Therapy Oncology Group / European Organisation for Research and Treatment Cancer (RTOG/EORTC) tool, is a formerly extensively used, validated tool for assessing acute toxicity resulting from therapeutic radiotherapy[67].

The original RTOG tool was developed in the early 1980s and was designed as a simple scoring scale aimed at giving a quick and objective assessment of a patient's degree of toxicity to radiotherapy. Radiation effects were graded on a categorical 0 – 5 scale, with score of '0' representing absence of symptoms and a score of '5' death. The RTOG tool is somewhat blunt in its assessment with large differences in severity of effect between grades. Further, it does not allow for the recording of emotional distress or social effects or impact of toxicity burden on quality of life. However, it has important historical context and has been widely used in clinical trials for the rapid assessment and capture of acute radiation-induced toxicity data.

In 1982 the RTOG tool was extended in collaboration with the EORTC to produce the joint RTOG/EORTC criteria for late toxicities in recognition of the need for a more standardised approach to reporting treatment-related toxicity, thus resulting in two scoring tools, the RTOG acute scale and RTOG/EORTC late toxicity scale[68]. A 90 day rule was created with a recommendation to use the acute RTOG tool for toxicities

emerging within 90 days of the start of radiotherapy and the RTOG/EORTC late tool to capture toxicities emerging more than 90 days from the start of treatment.

In 1998 The National Cancer Institute (NCI) developed version 2 of their Common Toxicity Criteria (CTC) in collaboration with the RTOG. This version of the tool which replaced the original (1983) version was extended from its original focus on chemotherapy-related toxicity, to include acute radiation-induced toxicities. As such CTC v2.0 quickly replaced the RTOG acute scale in many studies although the RTOG/EORTC late toxicity scale continued in use until late 2003 when the CTC v3.0 was developed. The new version of the CTC relabelled 'CTCAE v3.0' (Common Terminology Criteria for Adverse Events) encompassed both acute and late toxicities relating to chemotherapy and radiotherapy and resulted in the dropping of the old 90 day rule which was recognised as a somewhat arbitrary cut-off for the definition of acute versus late effects.

The CTCAE v3.0 was regarded as the first comprehensive multimodality grading system for reporting both acute and late effects in oncology and is the required toxicity scoring tool for all NCI-funded trails. In 2009, the fourth edition of the CTCAE was published and revised in 2010 and is available online. The 78-page revised document in essence constitutes a comprehensive standardised terminology, with accompanying categorical 0 – 5 grading system for reporting the scope and severity of treatment-induced events or toxicities covering 26 major organ systems. A total of 117 gastrointestinal 'adverse events' are listed covering the upper and lower gastrointestinal organs.

However, despite progress in achieving standardisation of toxicity nomenclature and reporting, a major criticism of the CTCAE is that in practice, there is no clear consensus as to how to score multiple signs and symptoms. Often, they are combined into a single (averaged) grade which, not least in studies where toxicity is a primary endpoint, is associated with a loss of specificity[42].

Whilst the focus of this thesis is the acute radiotherapy setting, one instrument designed for use in the late setting should be mentioned. The Subjective, Objective, Management, Analytic /Late Effects Normal Tissue (SOMA/LENT) system[69 70] was first published in 1995 by an expert working group within the EORTC/RTOG. As suggested by its acronym the characteristic feature of the system is that each toxicity item is classified by its subjective symptoms, objective signs and management-related or analytical measures[71]. Scoring is performed by healthcare professionals, based upon an interview and clinical examination.

Whilst this system embodies patient and clinician rated signs and symptoms of toxicity the problem of how to derive an aggregate score from a series of scores obtained for each individual aspect of toxicity is (as with the CTCAE) debated and there is obvious loss of fidelity in the aggregation process. Never-the-less the 'LENT-SOMA' system was the first attempt to produce a single comprehensive scoring tool incorporating both clinician and patient (subjective) scoring of toxicity[51]. LENT-SOMA items (including subjective elements) were incorporated within CTCAE v3.0, published in 2003[51].

1.2.5.2 An alternative tool for scoring symptoms from gastroenterology

One validated gastrointestinal scoring tool that has been used quite extensively in the UK[72] and has performed well in validation studies against the RTOG /EORTC lower GI including pelvis toxicity morbidity scoring criteria in both the acute[6] and late[73] radiotherapy setting is the Inflammatory Bowel Disease Questionnaire (IBDQ) and integral Bowel sub-set of questions (IBDQ-B).

The IBDQ was originally developed as a disease-specific measure of quality of life for patients with inflammatory bowel disease. It consists of four sub-scales of which bowel symptoms (IBDQ-B) form a subset of ten questions. A maximum score of 7 (absence of symptoms) and a minimum score of 1 (symptoms worse than ever before) is given for responses to each question thus allowing a maximum attainable score of 70 and a minimum score of 10 for the IBDQ-B subset. A fall in score between measurement time-points is indicative of worsening symptoms. The entire IBDQ (all sub-scales)

comprises 32 questions, following the same scoring system as the IBDQ-B with a maximum 224 points (Quality of Life best score) and a minimum 32 points (worst score). A fall in score between time-points is indicative of worsening quality of life.

The IBDQ questionnaire has been used to assess treatment-induced toxicity in six previous cohorts of patients with mixed pelvic malignancy receiving radiotherapy[6 24 46 74-76]. In these previous studies, the change in IBDQ-B score has ranged from a fall of 7.2 to 10.8 points from the start to the end of radiotherapy (**Table 1.9**). This equates to a 12 to 18% change in score out of a total possible 60 point change in score between the maximum (70 points) to minimum (10 points) scores attainable.

Table 1.9 Change in IBDQ-B Scores in previous pelvic cancer cohorts

Study, Reference Measurement	***IBDQ-B Scores***			***Cohort description (n)*** ***U: Urological; Gi: Gastrointestinal Gy: Gynaecological***
	Start-RT	**End-RT**	**Change**	
Khalid, 2006[6] Median (range)	69 (44 - 70)	61 (33 - 70)	- 8	107 U: 39; Gi: 30; Gy: 38
McGough, 2008[74] Median (range)	68 (54 - 70)	59 (35 - 69)	- 9	50 U: 16; Gi: 13; Gy: 21
Wedlake, 2008[24] Mean (sd)	66.6 (5.2)	56.9 (9.5)	- 9.7	59 U: 26; Gi: 6; Gy: 30
Wedlake, 2010[46] Mean (sd)	66.4 (7.7)	56.8 (9.4)	- 9.6	193 U: 101; Gi: 28; Gy: 64
McNair, 2011[75] Mean (sd)	68.9 (2.2)	58.1 (11.7)	- 10.8	21 U: 21 (Prostate)
Wedlake, 2012[76] Mean (sd)	66.1 (5.6)	58.9 (9.3)	- 7.2	117 U: 56; Gi: 38; Gy: 23

This description of toxicity scoring tools concludes a summary of the clinical setting within which the research described in this thesis takes place. The following sections of

this chapter explore the extent to which radiation-induced gastrointestinal toxicity and another inflammatory condition of the gastrointestinal tract, Inflammatory Bowel Disease (IBD) are similar and thus may benefit from similar management strategies.

The rationale for specific nutritional interventions in patients receiving pelvic radiotherapy with the aim of damping the inflammatory response, thus reducing clinical symptoms associated with acute treatment-induced toxicity, is examined.

1.3 Radiotherapy-induced gastrointestinal toxicity and Inflammatory Bowel Disease: Comparable diseases?

1.3.1 Introduction

It could be argued that acute radiation-induced gastrointestinal toxicity and IBD are comparable diseases in as much as gastrointestinal inflammation is the hallmark of both. If parallels can be drawn between the inflammatory mechanisms in these two diseases, it follows that strategies designed to prevent or reduce gastrointestinal inflammation in IBD may be applicable and transferrable to acute radiation-induced gastrointestinal toxicity, from this point referred to as 'radiation-induced GI toxicity'.

IBD is perhaps a 'gold standard' model of inflammation. It is certainly the most researched model of gastrointestinal inflammation and a condition in which nutritional strategies for the prevention of inflammation have been widely explored. Approximately 1.4 million Americans are affected by IBD[77] a figure remarkably similar to recent estimates of the prevalence of chronic bowel dysfunction following therapeutic pelvic irradiation in the US of 1.5-2 million[78].

IBD is a multi-factorial disorder which has been extensively studied. In contrast, pelvic radiation disease[13] has only recently begun to receive the degree of attention in keeping with its prevalence. This is despite the fact that radiation-induced gastrointestinal toxicity was first described over 100 years ago by Walsh in 1897 as '*inflammation of the gastrointestinal mucous membranes*' soon after Roentgen's description of X-rays[79].

This section explores the similarities between radiation-induced GI toxicity and IBD with the aim of providing a rationale to argue that these diseases display many similarities and that knowledge regarding the nutritional management of IBD can be usefully extrapolated to radiation-induced GI toxicity.

1.3.2 Aetiology, histology and clinical presentation of IBD and radiation-induced GI toxicity

1.3.2.1 Inflammatory Bowel Disease

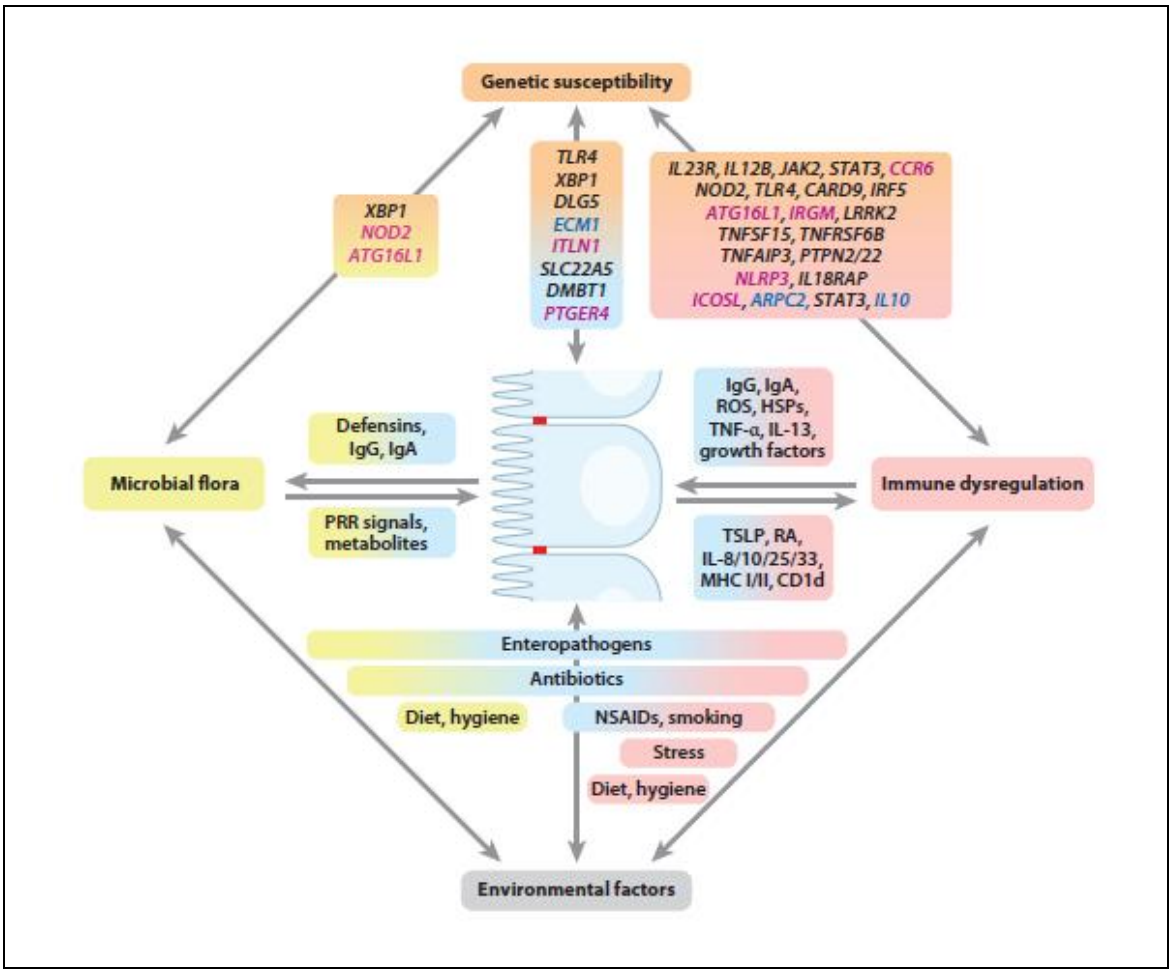
The idiopathic inflammatory bowel diseases (IBD) comprise two major forms of chronic intestinal inflammatory disorders, Crohn's disease (CD) and ulcerative colitis (UC). A third condition, pouchitis, is a complication of ileal pouch-anal anastomosis following colectomy in UC patients.

The incidence of Crohn's disease at 5-6 per 100,000 is rising slightly and varies country to country (Male: Female ratio of 1 : 1.2) whilst that of ulcerative colitis at 6-15 per 100,000 (Male: Female ratio of 1.2 : 1) is currently stable[80].

It has long been appreciated that the aetiology of IBD has a genetic component[80]. It is now acknowledged that IBD results from an inappropriate inflammatory response to intestinal microbiota in genetically susceptible individuals[77].

In addition to genetic susceptibility, the development and course of IBD is affected by gut microbiota, immune dysregulation and environmental factors[80]. There is substantial overlap in susceptibility gene loci for CD and UC. Some loci are unique to each disease (**Figure 1.2**).

Figure 1.2 Factors affecting the course and development of IBD.



Source: Kaser[80]. **Key:** Factors common to CD and UC in black font, CD-specific polymorphisms in ***magenta***, UC-specific polymorphisms in ***blue*** font, for abbreviations see glossary.

Heritable risk for IBD shows greater phenotypic concordance in monozygotic than dizygotic twins for both CD and UC with considerably higher concordance for CD (50-75%) compared to UC (10-20%) suggesting a greater role for environmental factors in UC [80 81]. In familial studies, 10-20% of individuals with IBD report one or more relatives also having the disease[82]. The relative risk of familial occurrence in European populations (i.e. prevalence of IBD among first degree relatives divided by the population prevalence) is approximately 15-fold[83].

Peak onset of CD is between 20 - 30 years of age with a second minor peak at 50 - 60 years. Peak onset of UC is between 20 - 40 years with a later minor peak at 60+ years.

Smokers are at increased risk of CD and former and non-smokers are at greater risk of UC. IBD carries increased risk of primary sclerosing cholangitis, ankylosing spondylitis and psoriasis[77]. A recent review suggested that patients with IBD have a 29 - 46% increased risk of severe acute toxicity or chronic complications following therapeutic radiotherapy[84].

Disease site in CD is most frequently the ileum and colon although any part of the intestine may be affected. In UC, site of disease is almost always the rectum (95% of patients) with varying degrees of proximal extension[83]. The inflammatory pattern in CD is typically patchy and transmural with lesions from the mucosa into the underlying serosa. Small superficial (aphthoid) ulcerations over Peyer's patches may be seen with deep focal inflammation sometimes accompanied by non-caseating granulomas[83]. Fistula formation and strictures are chronic complications.

The inflammatory pattern in UC is continuous and generally confined to the mucosa with ulceration, oedema and haemorrhage of varying severity. There is increased intestinal permeability as a result defective regulation and sealing of tight junctions. Defective Paneth and goblet cell function further compromises barrier integrity[77]. In ileal CD, Paneth cell secretion of anti-microbial α-defensins is reduced, whilst in colonic CD, expression of β-defensins is inadequate[85]. In UC, production of mucus is reduced due to insufficient differentiation of stem cells to goblet cells[85].

Clinical symptoms of IBD vary but can have a profound impact on patients' quality of life[86]. In CD symptoms reflect the location, extent and severity of disease and include diarrhoea, bile salt malabsorption (following terminal ileum resection) small bowel malabsorption of nutrients and vitamins, weight loss, anorexia and abdominal pain[83].

In contrast, bloody diarrhoea or passage of blood and mucus are cardinal symptoms of UC and present in over 90% of patients at presentation. Other symptoms of UC include urgency, tenesmus (sensation of needing to pass stool when no stool is present) and nocturnal diarrhoea. Cramping or abdominal pain may be mild or absent and unlike CD, weight loss is not usually a feature at presentation.

1.3.2.2 Radiation-induced GI toxicity

The aetiology of acute clinical radiation-induced GI toxicity is multifactorial[22]. Susceptibility genes for increased risk of severe toxicity have not been definitively identified. A recent validation study (n=1613) of 92 single nucleotide polymorphisms (SNPs) in 46 previously identified 'DNA damage and repair' genes concluded that, on reanalysis, none were significantly associated with late radiation toxicity[87]. Rare syndromes (*Nijmegen breakage syndrome*, *Fanconianaemia*, and *ataxia telangiectasia*) predispose to increased radio-sensitivity[17]. The role of patient and lifestyle factors is poorly defined with no high quality prospective studies. Smoking, low Body Mass Index (BMI), connective tissue disorders, auto-immune pathologies, vascular disorders and diabetes may also affect toxicity outcomes[46 78].

Ionising radiation provokes an acute inflammatory response in irradiated cells via reactive oxygen species (ROS) from the interaction of electrons and cellular water. ROS-mediated damage includes single and double strand DNA breaks and structural disruption of proteins, lipids and carbohydrates[18 88]. Down-stream cellular effects include cellular apoptosis, necrosis, mitotic catastrophe and phenotypic modification[89].

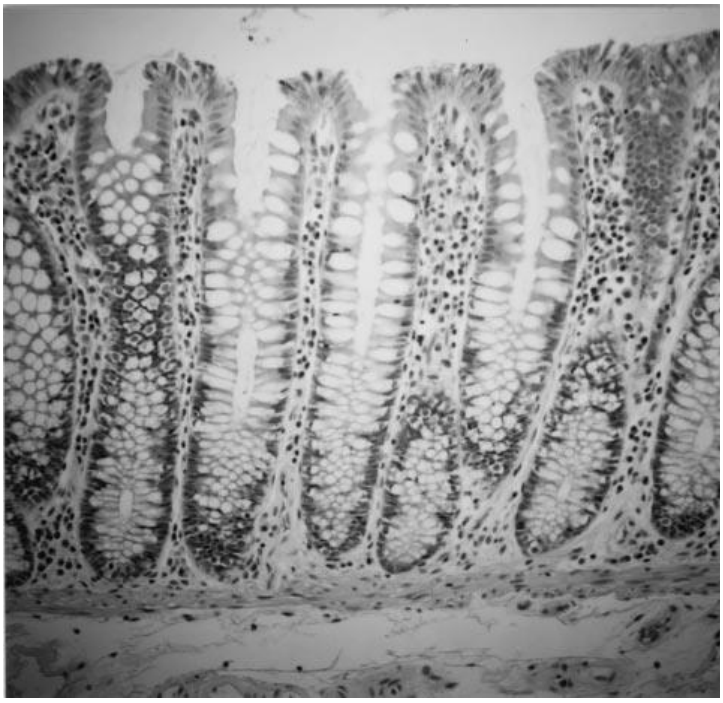
Unlike IBD, onset of radiation-induced damage can be precisely determined. In preclinical studies, mitotic inhibition (G_2 block) of stem cell differentiation has been reported within 30 minutes of radiation exposure with consequent changes in cell kinetics[90] and severely depleted crypt mitotic counts[91]. Apoptotic cells appear within 2 - 3 hours of irradiation[90] and are seen in crypts of the small and large intestine at one week[91]. In clinical fractionated delivery, repeated exposure leads to accumulating damage against a backdrop of incomplete repair[18]. The result is that normal tissue that is irradiated at the start of radiotherapy is qualitatively very different to the 'normal' tissue that is irradiated towards the end[18].

Preclinical studies investigating the effects of radiation on small intestinal morphology in rodent models have shown reduced crypt circumference, mucosal atrophy, grossly abnormal epithelial cells, decreased villus height and surface area, abnormalities in microvilli structure and goblet cell disorganisation and degeneration[90 91]. Similar

morphological features are observed in IBD. Derangement of tight junction protein occludin has also been reported with increased paracellular permeability. In vitro studies using marker molecules have confirmed increased intestinal permeability in irradiated human rectal tissue[92].

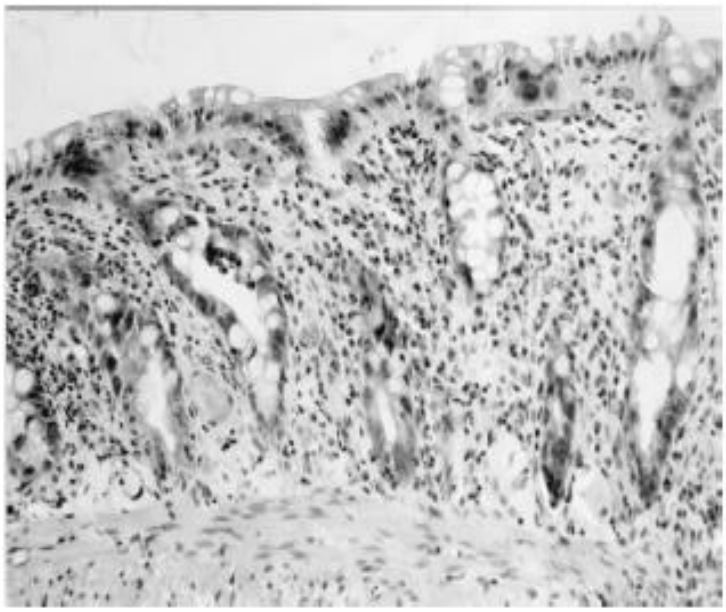
Sequential investigations[20 22 23] of rectal morphology in patients receiving pelvic radiotherapy for prostate cancer with biopsies taken at baseline (prior to start of radiotherapy) and after two and six weeks of fractionated radiotherapy have elegantly revealed the extent of change that occurs after just two weeks of fractionated radiotherapy treatment (**Figures 1.3a**, **1.3b**).

Figure 1.3a Normal rectal epithelium prior to radiotherapy



Source: Hovdenak[20]

Figure 1.3b Gland distortion and cryptitis following 18 Gray of radiotherapy



Source: Hovdenak[20]

In the Hovdenak study, maximum histological damage was evident at two weeks in contrast to symptoms, the prevalence and number of which rose throughout treatment[20]. Invasion of epithelial, glandular and stromal rectal tissue with neutrophils and eosinophilic granulocytes was seen with macrophages in the deeper lamina propria[20].

Congestion of the lamina propria with innate and adaptive immune cells and eosinophilic and neutrophilic abscesses has also been observed in-vitro in irradiated human rectal tissue[93].

Depletion of glands, defective barrier function and atrophy of surface epithelium all result in disruption to secretary and absorptive functions, effects on gastrointestinal physiology and resulting clinical symptoms.

1.3.3 Molecular mechanisms of inflammation and immune-mediated effects in IBD and radiation-induced GI toxicity

1.3.3.1 Introductory comments

A number of molecular mediators of inflammation are common to radiation-induced toxicity and IBD. They include cytokines, growth factors, integrins, cellular receptors and signalling pathway proteins. Their role in IBD has been extensively studied.

However, it was not until more recently that their role in radiation-induced GI toxicity was more fully understood to the extent that it is now described as an immuno-inflammatory response in a particularly radiosensitive body compartment, in which the gut microbiota plays a key role[89].

1.3.3.2 Inflammatory mediators: Inflammatory Bowel Disease

The stimulus for onset of IBD is not known but the concept that resident microbiota are largely tolerated whilst pathogenic species are targeted for destruction is not entirely correct[94]. In health, the intestinal lamina propria contains a mixed population of innate and adaptive immune system cells. Continual microbial sensing of resident and emergent microbiota is important in regulating the intestinal immune response[94].

To this end, epithelial cells, dendritic cells and macrophages (as components of the innate immune system) display pattern recognition receptors (PRRs) that recognise general microbial patters[77]. This contrasts with antigen-specific recognition in which IgA antibodies secreted by B plasma cells of the adaptive immune system contribute to host protection without provoking inflammation[94].

Toll-like receptors (TLRs) of which at least 12 have been described and intra-cellular nucleotide oligomerisation domains (NODs) recognise conserved microbial structures or pathogen-associated molecular patterns (PAMPs) and can respond to both pathogenic and harmless resident microbes with constitutive antimicrobial mechanisms[94]. Activation of TLRs induces various pathways that mediate microbial killing and activate adaptive cells. Activation of the NOD2 protein by bacterial peptidoglycan activates nuclear factor κB (NF-κB) and the mitogen-activated protein

kinase (MAPK) signalling pathway which in turn leads to production of tumour necrosis factor (TNF), interleukin-1β and anti-microbial peptides.

Most importantly, perturbation of the homeostatic balance between defence and tolerance is thought to be the critical factor predisposing to IBD[94]. In active IBD, inadequate resolution of inflammation and continued epithelial injury facilitates increased microbiota exposure which perpetuates the disease process[77].

In health, the innate and adaptive immune systems work together to regulate the immune response and prevent over-activation of defensive or inflammatory strategies. Dendritic cells present antigens to naïve CD4+T cells in gastrointestinal lymphoid tissue (GALT) where their phenotype and local cytokine environment moderates differentiation into T cell subgroups of helper (Th1, Th2 and Th17) and regulatory (Treg) cells. Activated T helper cells then circulate to the lamina propria, secrete their own compliment of inflammatory cytokines and carry out effector functions. Regulation of these T cell sub-groups must be continually fine-tuned to maintain intestinal homeostasis.

In active IBD, there is pronounced infiltration of the lamina propria with innate immune cells (neutrophils, macrophages, dendritic cells and natural killer T cells) and adaptive immune (B and T) cells[77 83]. This phenomena is similar to that observed (and described earlier) by Hovdenak[20]. Increased activation of these cells elevate local levels of pro-inflammatory tumour necrosis factor α (TNF-α), interleukin (IL) 1β, interferon-γ and cytokines of the interleukin-23-Th17 pathway[94]. The resulting imbalance between these and anti-inflammatory cytokines, transforming growth factor β (TGF-β), cytokine interleukin-10 (IL-10) and regulatory Treg cells (differentiation of which is regulated by TGF-β, IL-10 and retinoic acid) predisposes to a pro-inflammatory environment[94].

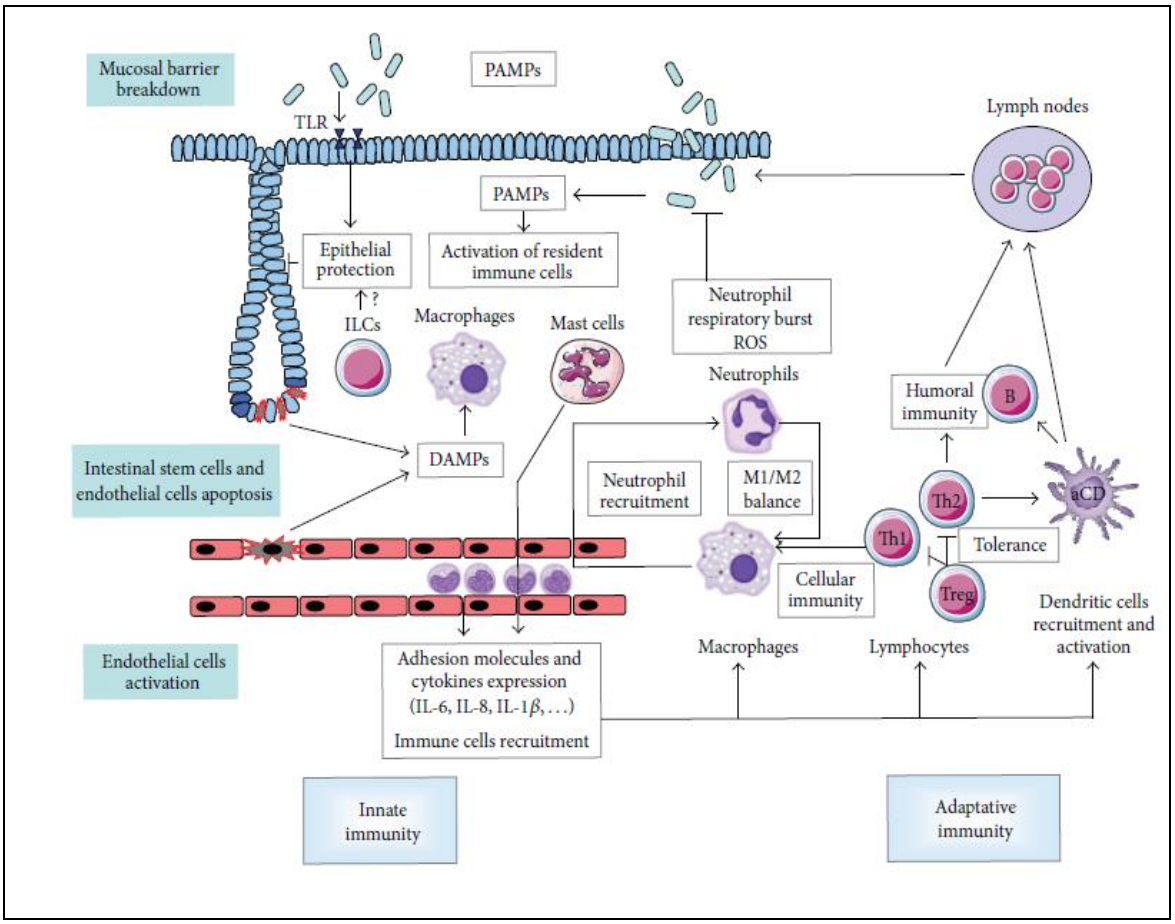
Up-regulation of adhesion molecules on vascular endothelial cells by elevated TNF-α and IL-1β causes increased leucocyte attraction and adherence with consequent abnormalities in intestinal microvasculature including ischemia, local tissue hypoxia, ongoing mucosal inflammation and impaired mucosal healing[77 94].

1.3.3.3 Inflammatory mediators: radiation-induced GI toxicity

As in IBD, recent evidence suggests that normal tissue inflammatory responses to irradiation are, as in IBD, inextricably linked to innate and adaptive immunity[95]. Damaged self-molecules or damage-associated molecular patterns (DAMPs), in a similar manner to PAMPs, are recognised and dealt with by the same immune pathways that orchestrate the host response to microbial and other threats.

In contrast to IBD where the initial inflammatory stimulus is not known, ionising radiation is a pro-inflammatory signal, the initiation of which can be precisely documented. In a similar manner to IBD, radiation-induced GI toxicity is now thought to involve the full repertoire of innate and adaptive immune responses (**Figure 1.4**)[89].

Figure 1.4 Inflammatory mediators in the response to ionising radiation



Source: Francois[89]

TLRs present on epithelial cells respond to DAMPs including high-mobility-group box 1 (HMGB1) proteins, heat shock proteins and proteins damaged by reactive oxygen species (ROS)[95]. DAMP-activation of TLRs results in translocation of transcription factor NF-κB, which in the inactive state is sequestered in the cytoplasm, and activator protein-1 (AP-1). Translocation results in transcription of pro-inflammatory cytokines similar to those observed in IBD including IL-1β, IL-6, IL-8 and TNF-α[96]. In pre-clinical models, radiation exposure has been demonstrated to increase TLR expression and enhanced expression of interleukin-12 (IL-12) and interleukin-18 (IL-18)[97].

Mast cells are resident immune cells in the gut, capable of mounting a particularly rapid response to various physiological and pathological stimuli with vigorous secretion of pro-inflammatory, vasoactive and mitogenic mediators[89]. Rapid proliferation of mast cells has been observed in mucosa and submucosa following radiotherapy for rectal carcinoma[89].

As in IBD, endothelial dysfunction has been reported in the pathogenesis of early and late radiation damage[98]. Endothelial cells form the inner lining of blood vessels representing a total surface area of 4000-7000m^2 and under normal conditions maintain an antithrombotic and anticoagulant balance by exerting molecular control over platelet aggregation, coagulation and fibrinolysis[98].

Marked loss of thromboresistance occurs following exposure to ionising radiation as radiation causes a deficiency in thrombomodulin (TM) which results in insufficient activation of protein C, a plasma protein with anti-coagulant, anti-inflammatory, and cytoprotective properties thus potentiating a pro-inflammatory vascular environment[98].

Other work has shown the importance of leukocyte recruitment in exacerbating damage mediated by vascular adhesion molecules (ICAM-1 and VCAM-1) and leukocyte adhesion receptors, selectins 'L', 'P' and 'E'[99-101]. Increased expression of ICAM-1 in response to ionising radiation has also been reported in IBD patients[101] and up-regulation of adhesion molecules has similarly been reported in IBD.

Pre-clinical intravital microscopy studies have reported involvement of the p38 MAPK and rho kinase (ROCK) signalling pathways in radiotherapy-induced vascular inflammation with increased platelet recruitment, leucocyte rolling, adhesion and increased myeloperoxidase 'MPO' and CXC chemokines[102 103].

Increased colonic permeability has also been reported suggesting more wide-spread effects of MAPK and ROCK signalling. Increased activation of p38 MAPK signalling pathways in response to ionising radiation[104] has also been observed in patients with inflammatory bowel disease[105].

As with IBD, perturbation of the balance between pro-and anti-inflammatory cytokines in radiation-induced GI toxicity may be particularly important in perpetuating the pro-inflammatory response. In a pre-clinical model using rat ileal muscularis tissue, radiation exposure caused rapid translocation of NF-κB sub-units p65 and p50 to the nucleus with increased transcription of proinflammatory IL-1β, TNF-α, IL-6 and cytokine-induced neutrophil chemoattractant (CINC) resulting in an imbalance in interleukin 1 receptor antagonist (IL-1ra) and IL-10[96]. An imbalance between IL-1β and IL-1ra has been reported to be an important factor in the pathogenesis of IBD[96].

Much of the early work in radiation-induced toxicity focussed on the role of specific inflammatory mediators. However, more recent research in this area, in common with IBD, has focussed on the elucidation of immuno-inflammatory processes[89 95]. In radiation-induced toxicity eicosanoids were initially identified as mediators of vascular damage with significant increases in the levels leukotriene B_4, (LTB_4), thromboxane B_2 (TXB_2) and prostaglandin E_2 (PGE2) found in rectal dialysate following pelvic radiotherapy[106]. However, these findings have not been repeated[23].

Other studies have observed increased expression of cyclooxygenase-1 and 2 (Cox-1, Cox-2) and NF-κB[91 93], in pre-clinical [91] and ex-vivo irradiated colorectal tissue[93]; significantly upregulated mRNA levels of IL-1β, Il-6 and TNF-α in irradiated rat colon and jejenum[107]; significantly increased IFN-ɣ and IL-6 in proteonomic profiling of peripheral blood from patients undergoing IMRT for prostate cancer[108]; significantly

elevated IL-6 in prostate cancer patients on day 15 of radiotherapy[109] and positive correlations between IL-6, matrix metalloproteinase 9 (MMP-9), platelet derived growth factor (PDGF) and symptom scores assessed using the IBDQ-B tool in patients receiving pelvic radiotherapy[66].

1.3.4 Microbiota and gastrointestinal inflammation in IBD and radiation-induced GI toxicity

1.3.4.1 Introductory comments

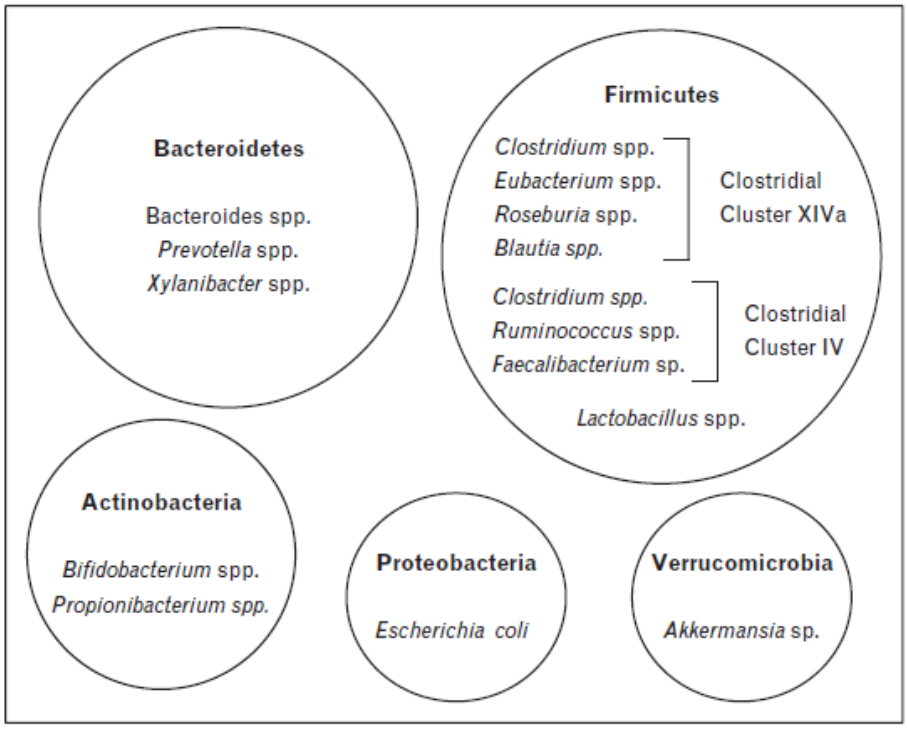
Culture-independent techniques and computational taxonomy has enabled dramatic improvements in our understanding of the bacteria (microbiota) that inhabit the gut and the crucial role they play in gastrointestinal inflammatory processes. The human gastrointestinal tract has a mucosal surface area of 300 – 400 m^2 (similar in size to a tennis court)[110]. In absolute terms it harbours more than 10^{14} microorganisms the majority of which (10^{11} cells/g) inhabit the colon.

In total, the microbiota comprises over 1000 prevalent bacterial species with a biomass of over 1kg and at least 160 species per individual[111]. In health it seems an individual's microbiota, especially mucosa-associated communities are relatively stable over time[110].

Microbiota composition is influenced by birth (caesarean section *versus* vaginal delivery) breastfeeding, diet and therapeutic intervention. By 2.5 years of age, an infant's microbial community resembles that of an adult[112]. The mix of microbiota species influences metabolic capability (metabolomics) which includes vitamin synthesis, bile salt metabolism, xenobiotic degradation and carbohydrate fermentation and resulting production of SCFA[111].

In health, anaerobes are several orders of magnitude more abundant than aerobes with the predominant species belonging to five major phyla (**Figure 1.5**).

Figure 1.5 Predominant species of the human colonic microbiota



Source: Reference[113]

1.3.4.2 Inflammatory Bowel Disease

Dysbiosis (perturbation in the microbiota) is associated with the pathogenesis of IBD although it is unclear whether this is a cause or effect of disease. Evidence indicates that the presence of gut bacteria is a necessary pre-requisite for an immune-inflammatory response[110]. In CD, diversion of the faecal stream induces remission whilst reinfusion of intestinal contents reactivates disease, in UC, broad-spectrum antibiotics can reduce metabolic activity of microbiota and mucosal inflammation[110].

However, whilst microbiota can drive inflammation, the opposite is also true. Pre-clinical studies show that microbiota metabolites, SCFA can moderate immune responses by suppression of transcription activator NF-κB or promotion of the expansion of the anti-inflammatory Treg cell populations.

Dysbiosisis in IBD is characterised by a reduction in overall microbiota diversity and over- or under-expression of individual species (**Figures 1.6a and 1.6b**).

Figure 1.6a Dysbiosis in UC patients

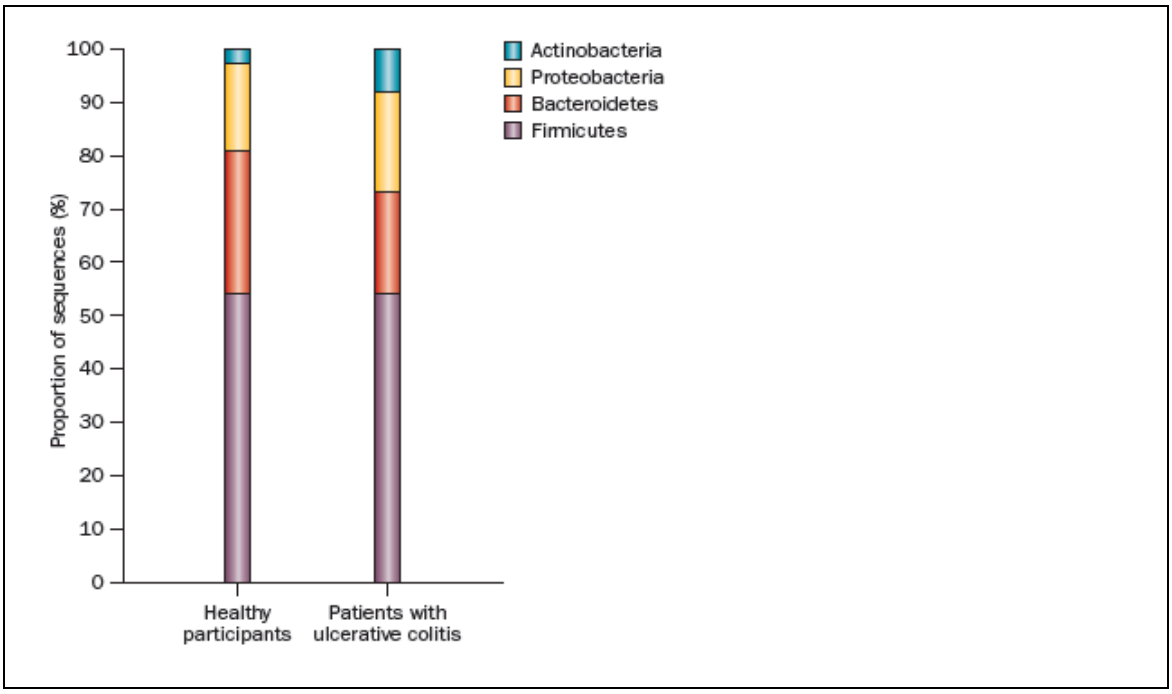
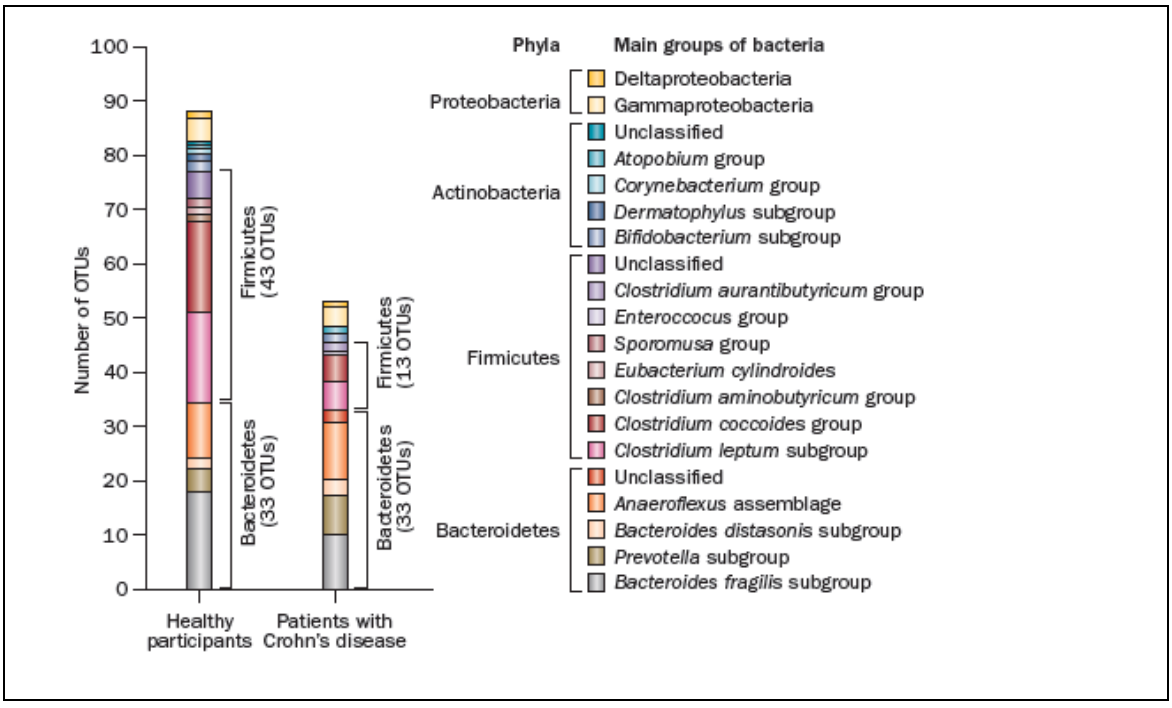


Figure 1.6b Reduction in bacterial diversity in CD patients



Source: Manichanh[110]

Reduced numbers of Bacteroides in UC and pouchitis patients, Firmicutes and Roseburia in CD and UC patients and *Faecalibacterium prausnitzii* in CD, UC and pouchitis patients has been observed[110 114].

In contrast, increases in Proteobacteria in UC and pouchitis patients, Enterobacteria in UC and CD patients, Actinobacteria in UC patients[110] and Ruminococcus, Bifidobacterium and Lactobacillus in CD patients have been reported[110 115]. A new pathogenic strain of E. coli, 'adherent-invasive E. coli' (AIEC) has been found in CD patients and in UC increased gram-negative, crypt-associated, anaerobic sulphate-reducing bacteria have been observed[110].

In CD and UC there is decreased stability in the mix of species. Sequential faecal sampling in UC patients has shown that only one third of dominant taxa are consistently detected over time[110]. Change in composition is associated with striking changes in metabolic pathways and products. A recent analysis in 231 IBD patients reported that even small (2%) changes in genera resulted in a 12% change in metabolic pathways including reduced SCFA production[116].

1.3.4.3 Radiation-induced GI toxicity

Few studies have examined the direct effects of radiation on the intestinal microbiota. One pre-clinical study (available in abstract only) reported 'postradiation dysbacteriosis' with decreased Lactobacilli and Bifidobacteria and a concomitant increase in Escherichia, Proteus and Clostridium in guinea pigs subjected to irradiation[117].

A notable recent pilot study comprising 10 patients undergoing fractionated radiotherapy for pelvic malignancies used cluster analysis to investigate the similarity in bacterial profiles of patients who developed new-onset diarrhoea[48] *versus* those who remained diarrhoea-free. The six patients reporting new-onset diarrhoea (graded using Common Toxicity Criteria for reporting Adverse Events 'CTCAE' v.2) showed a significantly modified bacterial profile ($p<0.05$) and clustered separately from those who remained diarrhoea-free. Sub-group analysis further revealed increased Actinobacteria and Bacilli in the two patients reporting worst diarrhoea[48].

Another pilot study from our group in collaboration with Coventry University used electronic nose (e-nose) technology and Field Asymmetric Ion Mobility Spectrometry (FAIMS) in 23 patients undergoing pelvic radiotherapy. Patients who reported the worst on-treatment symptoms (scored using the IBDQ-B) clustered separately on the basis of their fermentone profile (volatiles emitted from faecal samples) from those who reported least toxicity *before* and *after* treatment, suggesting predictive benefits of the e-nose technology[49].

It has been reported that this technology may be equally relevant for diagnostic or predictive purposes in other inflammatory conditions such as IBD[118]. Evidence of the adverse impact of irradiation on gut motility and consequent outcomes such as small intestinal bacterial overgrowth (SIBO) has long been recognised particularly in late (post-radiation) 'enteropathy'[119]. In the acute setting, our group used glucose hydrogen breath testing to test for SIBO in 39 patients receiving pelvic radiotherapy and reported that 26% developed new-onset glucose intolerance, indicative of SIBO[27].

Preclinical studies provide evidence of a dynamic interaction between the host microbiota and the innate immune system in modulating the intestinal response to radiation[120]. Germ-free mice show increased radiation resistance with fewer apoptotic endothelial cells and lymphocytes in small intestinal villi cores than conventionally raised animals[121]. Paradoxically, though, lipopolysaccharide (LPS) a component of the external membrane of gram-negative bacteria and a ligand for TLR4 is radio-protective, reducing crypt cell apoptosis and improving intestinal crypt cell survival through a prostaglandin-mediated mechanism[122-124].

Flagellin, a component of flagellated bacteria and a ligand for TLR5 is also radio-protective against sub-lethal doses of whole body irradiation in mice and primates[89] [120]. *Lactobacillus rhamnosus* GG administered prophylactically improved crypt survival and reduced epithelial apoptosis in wild-type but not TLR2 / MyD88 / COX-2 knock-out animals, suggesting a TLR2/MyD88 mediated mechanism that involved a repositioning of constitutive COX-2 expressing mesenchymal stem cells to the crypt base[122].

1.3.5 Summary: similarities between IBD and radiation-induced gastrointestinal inflammation

This section has compared the mechanism and mediators of gastrointestinal inflammation in IBD with those known to occur in radiation-induced GI toxicity and found many similarities between these two inflammatory conditions.

Whilst the aetiologies of IBD and radiation-induced GI toxicity are quite distinct, there are specific aspects of IBD that closely resemble radiation-induced GI toxicity. Therefore, it is concluded that sufficient similarities exist in histology, clinical presentation and molecular mediators of inflammation to indicate that management strategies, appropriate to IBD may also be applicable to radiation-induced GI toxicity. Since nutritional strategies have been widely explored in IBD, it follows that they might also be helpful in radiation-induced GI toxicity.

The next step in this introduction is to explore nutritional strategies, with particular emphasis on their potential impact on inflammatory mechanisms that may be potentially beneficial. Since the clinical interest of this thesis is directed towards patients receiving pelvic radiotherapy, the emphasis will be on strategies which may show promise in this setting.

1.4 Novel nutritional strategies for the prevention of gastrointestinal inflammation

1.4.1 Introduction

No pharmacological preparations have been approved for prevention or treatment of gastrointestinal inflammation during pelvic radiotherapy[125]. Nutritional intervention is popular with patients who have amply demonstrated that they are capable of following dietary prescriptions for extended periods in this setting[75 126]. In the last decade, two systematic reviews[127 128] including a recent review by our group[127] and one meta-analysis[129] have been conducted exploring the efficacy of nutritional interventions in patients receiving pelvic radiotherapy.

Interventions have included elemental formulas (pre-hydrolysed enteral formulas), low or modified fat diets, lactose-restricted diets, probiotics and prebiotics and low residue or modified fibre diets. Whilst all of these interventions have a sound scientific rationale for use[127] and some have been trialled (with limited success) for the prevention or treatment of radiation-induced GI toxicity, there remains a lack of high grade evidence to recommend any one of these strategies over another during pelvic radiotherapy. Highly variable study quality, potential for bias, difficulties with compliance and palatability and lack of validated endpoints are acknowledged as problematic by all authors[127-129].

The sole meta-analysis of nutritional interventions, using a fixed effect model, based on 4 studies (n=413) returned a positive result for dietary intervention for the prevention of radiotherapy-induced diarrhoea, risk ratio of 0.66 (95% CI: 0.51 - 0.87)[129]. However all but one of the four studies used a combined intervention (e.g. a low fat plus low lactose diet) making it difficult to draw firm conclusions about the nature of the effective intervention[129]. Further, it could be argued that given the widely differing design of the interventions included in the analysis, a random effects model might have been more appropriate. One study included in the review was classified as therapeutic[130] although our group, on contact with the author has learned that this study was actually preventative in design and aim. The Cochrane meta-analysis did not include probiotic interventions. However, the two previous systematic reviews alluded to their possible benefits[127 128].

1.4.2 Importance and relevance of probiotic interventions

Probiotic interventions are relevant to radiation-induced GI toxicity via their ability to directly influence the host immune response, and thus inflammatory processes, through promotion of beneficial microbiota species. Recent guidelines from the Mucositis Study Group of the Multinational Association of Supportive Care in cancer / International Society of Oral Oncology (MASCC/ISOO) suggested that Lactobacillus-containing probiotic preparations might be helpful for the prevention of radiotherapy-

induced diarrhoea but declined to recommend specific doses or regimens[125]. This suggestion was based on evidence from five studies.

Two meta-analyses[131 132] have also examined the evidence for probiotic intervention in cancer patients receiving pelvic radiotherapy. The earlier analysis, based on four studies (n=632), using a random effects model, reported an odds ratio of 0.47 (95% CI: 0.13 – 1.67) in favour of probiotic intervention for the prevention of radiotherapy-induced diarrhoea but hesitated to draw firm conclusions or make specific recommendations due to clinical and statistical heterogeneity[131].

The more recent meta-analysis, based on ten studies (n=1449) of which six were included in the meta-analysis, reported an odds ratio for incidence of diarrhoea of 0.44 (95% CI: 0.21 – 0.92) in favour of probiotic supplementation and concluded a probable benefit[132]. Probiotic supplements vary widely in composition and strength and may be expected to have differing effects given the wide inter-individual variation in microbiota composition.

Although the safety profile of probiotic interventions appears to be good, rigorous safety testing employing high dose agents has not been conducted in the oncology setting and risk of translocation remains.

1.4.3 Dietary fibre

1.4.3.1 Introduction

Dietary fibre may mitigate inflammation during pelvic radiotherapy. Short chain fatty acids, the fermentation products of non-digested dietary fibre have direct anti-inflammatory effects, stimulate colonic water and sodium absorption, preserve tight junction integrity and provide a fuel source to colonic mucosa[133].

Despite this, patients receiving pelvic radiotherapy are often advised to reduce their dietary fibre consumption, which is also the case in some IBD centres. This practice is not evidence-based and may be counter-productive. This section defines what is

meant by the term 'dietary fibre' and discusses its potential importance for patients undergoing pelvic radiotherapy with respect to its impact on gut microbiota and production of fermentation metabolites, SCFA.

1.4.3.2 Definition, composition and recommended intakes

In 1972, dietary fibre was defined as 'the skeletal remains of plant cells that are resistant to digestion by enzymes of man'[134]. Whilst this concept still broadly meets the public perception of dietary fibre, the situation today is confusing because different definitions of dietary fibre are in use. This situation exists because historically two different methods for the analysis and definition of dietary fibre have been used: the enzymatic-gravimetric and the enzymatic-chemical methods.

The enzymatic-gravimetric method estimates total dietary fibre in foods by a series of steps including: enzymatic hydrolysis of proteins, sugars and starches; precipitation of soluble fibre components by aqueous ethanol; isolation and weighing of the dietary fibre residue and final correction for protein and ash in the residue[135]. The method has been adopted, simplified and modified by the Association of Official Analytical Chemists (AOAC) and is used in the US as the basis of food composition tables[136]. It is in widespread use, with minor modifications, in many countries.

The enzymatic-chemical or Englyst method also starts with the enzymatic removal of starch but goes on to measure non-starch (i.e. non-α-glucan) polysaccharides (NSP) as the sum of the constituent individual monosaccharides (hexoses, pentoses, uronic acids) released by acid hydrolysis and measured using gas liquid chromatography or colorimetry[135]. Differences between the enzymatic-gravimetric and Englyst methods have important implications for public health recommendations and food labelling. The enzymatic-gravimetric method measures both lignin (a minor component of the diet but chemically not a carbohydrate) and resistant starch, neither of which is measured by the Englyst method.

Table 1.10 outlines some of the definitions of dietary fibre in use today by different organisations, illustrating the differing derivations of dietary fibre.

Table 1.10 Summary of selected definitions of dietary fibre

Organisation Date References	Method of analysis	Definition
Codex Committee on Nutrition and Foods for Special Dietary Purposes (CCNFSDU)[137] **FAO/WHO Codex Alimentarius Commission 2008[138]**	*Enzymatic-gravimetric. Based on AOAC methods 985.29 and supporting AOAC methods*	**Dietary fibre** means carbohydrate polymers with ten or more monomeric units, which are not hydrolysed by the endogenous enzymes in the small intestine of humans and belong to the following categories: **Edible carbohydrate polymers** naturally occurring in the food as consumed, **Carbohydrate polymers**, which have been obtained from food raw material by physical, enzymatic or chemical means and which have been shown to have a physiological effect of benefit to health as demonstrated by generally accepted scientific evidence to competent authorities, **Synthetic carbohydrate polymers** which have been shown to a have a physiological effect of benefit to health as demonstrated by generally accepted scientific evidence to competent authorities
European Commission 2008[138]	*Enzymatic-gravimetric. Based on AOAC methods 985.29 and supporting AOAC methods*	For the purposes of this directive **'fibre'** means carbohydrate polymers with three or more monomeric units, which are neither digested nor absorbed in the human small intestine and belong to the following categories: **Edible carbohydrate polymers** naturally occurring in the food as consumed, **Carbohydrate polymers**, which have been obtained from food raw material by physical, enzymatic or chemical means and which have a beneficial physiological effect demonstrated by generally accepted scientific evidence, **Edible synthetic carbohydrate polymers** which have a beneficial physiological effect demonstrated by generally accepted scientific evidence
Food and Nutrition Board Institute of Medicine US 2002[136]	*Enzymatic-gravimetric. Based on AOAC methods 985.29 and supporting AOAC methods*	**Dietary Fiber** consists of non-digestible carbohydrates and lignin that are intrinsic and intact in plants **Added Fiber** consists of isolated, nondigestible carbohydrates that have beneficial physiological effects in humans **Total Fiber** is the sum of **Dietary Fiber** and **Added Fiber**
Food Standards Agency, UK, 2000	*Enzymatic-gravimetric. Based on AOAC methods 985.29 and supporting AOAC methods*	**Dietary fibre** is the material isolated by AOAC methods 985.29 and /or 991.43 combined with 997.08
Committee on Medical aspects of Food (COMA) UK, 1991[139]	*Enzymatic-chemical*	**Dietary fibre** is non-starch polysaccharide as measured by the Englyst method

Of key importance is the fact that the enzymatic-gravimetric method results in a higher value for the fibre content of a food than the Englyst method. One gram of NSP is estimated to be equivalent to 1.6g of dietary fibre[140]. In addition, the enzymatic-gravimetric method recognises and includes synthetic and extracted substrates that behave like fibre provided they have proven physiological benefits thus increasing the discrepancy between fibre and NSP.

An important distinction exists between the CODEX[137] and European Commission definitions of dietary fibre[138] with respect to the degree of polymerisation (DP) of carbohydrate polymers (i.e. linear or branched chains of monomeric carbohydrate units) to qualify as dietary fibre. Whilst a carbohydrate polymer must be ≥ 10 monomeric units to classify as 'fibre' according to the CODEX definition, it need only have a DP of ≥3 monomeric units according to the European Commission, provided physiological benefit has been demonstrated (**Table 1.10**).

This means that the inulin-type fructans (e.g. oligofructose, fructooligosaccharides (FOS)) with DP 3-8 qualify as a fibre substrate according to the European Commission definition. Fructans are naturally occurring plant storage carbohydrates (wheat and onions constitute major dietary sources) which escape digestion in the small intestine which lacks the enzymes required to digest its β-(2-1) fructosyl-fructose glycosidic bonds[141].

Fructans are fermentable substrates and importantly has demonstrable prebiotic capability through its ability to selectively stimulate the growth of microbial genera or species of potential health benefit to the host[142]. Commercial fructans (i.e. FOS) can be synthetically manufactured from sucrose or chicory root and are added to pre-prepared foods for their textual and sensory properties. FOS, as a prebiotic substrate has also attracted attention for use in clinical research and in this respect constitutes a fibre supplement either in its own right or more commonly, mixed with inulin.

Non-starch polysaccharides in the human diet include cellulose and hemicellulose (plant cell walls), xylans (cereals), galactomannans (legumes), β-glucans (cereals),

inulin (onions, root vegetables and artichokes), pectins, gums and mucilages[140]. Each of these fractions of fibre has differing solubility. Cellulose and hemi-cellulose are insoluble in water, xylans and galactomannans partially soluble and inulin, pectin, gums and mucilages are all water soluble[140]. Most foods contain a mix of soluble and insoluble fractions. Insoluble fibre is poorly fermentable and has been described as chemically inert. However it increases faecal bulk and reduces bowel transit time thus contributing to bowel heath. Soluble fibre (capable of forming viscous gels) has a number of health benefits but importantly is readily fermentable by saccharolytic bacteria producing beneficial metabolites, SCFA.

The UK Dietary Reference Value (DRV) for fibre is based on NSP content and set at a level which aims to optimise bowel function and stool output at about 100 g / day [139]. In contrast, Guideline Daily Amounts (GDAs) in the UK used for nutritional labelling (to be superseded in 2014 by Reference Intakes in line with EU Regulation 1169/2011) are based on the fibre content of foods derived using the AOAC methods and result in higher values. Recommended intake of 'fiber' in the US (from government and professional organisations) is based on AOAC methods but given in terms of total energy intake as shown in **Table 1.11**[143 144].

Table 1.11 Recommended fibre intakes: UK and US

Organisation / Date	Recommended Intake
Committee on Medical aspects of Food (COMA) UK, 1991[139]	*Dietary Reference Value (men and women): 18 g NSP / day*
Institute of Grocery Distribution (IGD) UK, 1998[145]	*Guideline Daily Amount (men and women): 24 g fibre / day*
Academy of Nutrition and Dietetics US, 2008[143]	*Dietary Reference Intake (men and women): 14 g / 1000 kcal / day*
Institute of Medicine (IOM) Guidelines in: US Departments of Agriculture and Health and Human Service, 2010[144]	*Dietary guideline recommendations: 14 g / 1000 kcal / day* *Men: 34 g / day (19 – 30 yrs), 31 g / day (31 – 50 yrs), 28 g / d (51+ years)* *Women: 28 g / day (19 – 30 yrs), 25 g / day (31 – 50 yrs), 22 g / d (51+ years)*

1.4.3.3 Fibre, diet and microbiota

The major saccharolytic bacteria (i.e. capable of degrading fibre) are listed in **Table 1.12** together with their known substrate preferences[113].

Table 1.12 Fibre fractions and major bacterial utilisers

Substrate	Major bacterial utilisers
Cellulose	*Ruminococcus, Bacteroides*
Hemicelluloses	*Roseburia, Bacteroides, Prevotella*
Pectin	*Bacteroides, Faecalibacterium,*
Fructans, including: inulin and fructo-oligosaccharides 'FOS')	*Bacteroides, Roseburia, Faecalibacterium, Bifidobacterium*
Resistant starch	*Ruminococcus, Bacteroides*

Source: Based on Chassard[113]

Overall, microbiota composition reflects habitual diet but can change in response to dietary manipulation[146]. As such it represents an important target for therapeutic intervention[147]. Recently a unique locus encoding enzymes for degradation of xyloglucan (a plant polysaccharide widely occurring in salad and cereal crops) was discovered in Bacteroides ovatus underlining the importance of niche species in dietary fibre metabolism[148].

A cross sectional study in 98 individuals using both recent (recall) and long term (food frequency questionnaire) dietary assessments and 16SrDNA sequencing to characterise faecal bacteria, reported a clustering of faecal communities into two distinct groups: a Bacteroides-rich cluster associated with a high-fat / low-fibre intake and a Prevotella-rich cluster associated with low-fat / high fibre intakes[149]. Firmicutes and Bacteroidetes phyla were positively associated with fibre and negatively associated with fat intake.

However, a 10-day feeding trial in 10 subjects failed to demonstrate similar trends suggesting that longer-term changes were necessary to influence bacterial community structure[149]. In contrast, a recent 5-day dietary intervention reported that gut

microbial communities can change in a rapid, diet-specific manner[150]. A cross-over design was used to compare alterations in microbiota resulting from adherence to two diets characterised as either plant-based, with a fibre intake of 25.6 ± 1.1 g / 1000 kcal or animal-based, with fibre intake amounting to a trace only. Although marked changes in composition were observed only with the animal-based diet, including increased abundance of bile-tolerant organisms and decreased level of Firmicutes, a significant positive correlation was reported between subjects' fibre intake over the previous 12 months and baseline levels of Prevotella suggesting that habitual high-fibre diets induce saccharolytic species[150].

In another large study, using classical culture-based methods, faecal samples obtained from 144 vegetarians and 105 vegans were compared with samples from an equal number of age / gender matched controls consuming an omnivorous diet[151]. The total microbial count did not differ between groups. However, stool pH of subjects having vegan or vegetarian diets was significantly lower ($p=0.0001$) than those on the omnivorous diet and total counts of Bacteriodes, Bifidbacterium, *Escherichia coli* and Enterobacteria were all significantly lower in vegans compared to control subjects[151].

Another recent analysis of 178 elderly subjects found microbiota groupings were defined by residence (community dwelling versus residential care) and that these groupings were sustained when diet was used as the basis for grouping. The authors concluded that their data supported a relationship between diet, microbiota and health status pointing to the importance of diet-driven alterations in age-associated declining health status including what they termed 'immuno-senescence'[152].

1.4.4 Focus on short-chain fatty acids and therapeutic potential

1.4.4.1 Introduction

Short-chain fatty acids are the end products of the bacterial digestion of carbohydrates and peptides that reach the colon, with carbohydrates by far the most abundant substrate[153]. They have multiple effects on colonic health and physiology including

electrolyte and water absorption, regulation of inflammation, contribution to colonic pH and energy provision to colonocytes.

In healthy individuals, substrate type and availability, microbiota composition and intestinal transit time determine the character of SCFA produced. For example, bacteria of the Bacteroidetes phylum produce high levels of acetate and propionate whilst those of the Firmicutes phylum produce high amounts of butyrate[153]. Degree of fermentation varies with substrate solubility and ranges from 0 to 5% for lignin, 20% for cellulose, 70% for bran, 90 – 95% for pectin and psyllium and up to 100% for mono= and oligosaccharides[133].

The principal SCFAs resulting from carbohydrate degradation are straight chain fatty acids, comprising 2, 3 and 4 carbon ('C') chains. They are acetate (C2), propionate (C3) and butyrate (C4) in the relative proportion of 6:3:1 (141)[133]. SCFA concentration is highest in proximal colon, due to greater carbohydrate availability, ranging from 70 - 100 mM. Daily production of SCFA in healthy adults is estimated to be 100 – 200 mM, the majority of which is absorbed and used by colonocytes which have a preference for butyrate which is 70 – 90% metabolised. Concentrations in peripheral blood are much lower and in micromolar amounts[154].

Intake of dietary fibre has recently been directly associated with faecal SCFA concentrations[155]. Total, soluble and insoluble fibre intakes, assessed using a validated Food Frequency Questionnaire (FFQ) and faecal SCFA concentrations were measured in 32 institutionalised elderly subjects who consumed a mean 11.6 g of fibre / day of which 82% comprised insoluble fibre. Significant positive associations were reported between consumption of insoluble fibre (g/d) and faecal butyrate concentration (mg/g) (p=0.049) and between total fibre (g/d) and acetate and propionate (p=0.003 and p=0.004 respectively). The authors acknowledged the wide inter-subject variation in basal faecal butyrate levels that have been previously reported[156] but pointed out that subjects with low levels may constitute a particularly responsive group to intervention[155]. In healthy subjects, formula diets (comprising 100% of energy intake

for 14 days) supplemented with fructo-oligosaccharides and fibre maintained faecal SCFA concentrations[157] possibly mediated through *Faecalibacterium prausnitzii*[158].

1.4.4.2 Therapeutic potential of SCFA in gastrointestinal inflammation

Surprisingly, despite the acknowledged association between dietary fibre and the production of SCFA and the potentially crucial importance of SCFA in reducing the inflammatory response and promoting colonic fluid absorption, no studies have assessed the effect of dietary fibre on SCFA production and bowel-related toxicity during pelvic radiotherapy.

Five studies have investigated the efficacy of SCFA and butyrate enemas in the treatment of radiation-induced 'proctitis'. However, whilst the findings of these studies contribute to the body of research regarding the therapeutic potential of SCFA after pelvic radiation, the use of the term 'chronic proctitis' is considered inappropriate[159]. The suffix '*itis*', in medical terminology specifically describes an inflammatory process. Unlike IBD where inflammatory mechanisms in the gut mucosa predominate throughout the course of the disease, in the chronic post-radiotherapy setting, three months or more after treatment, sub-mucosal pathology, noteably fibrosis rather than mucosal inflammation is the predominant finding. Thus the term 'chronic proctopathy' is preferred and is used in this brief overview of relevant studies.

Three randomised, double-blind, placebo controlled trials (**Table 1.13**) have been conducted[160-162]. The most recent trial used a cross-over design and reported a significant improvement in post radiation proctopathy, assessed clinically and endoscopically for the butyrate enema arm compared to placebo[162]. However, an earlier randomised controlled trial (RCT) using a similar design in patients with persistent proctopathy one year after radiotherapy found no significant improvement in the treatment group versus placebo[160].

A third RCT using a combined SCFA enema for the treatment of chronic proctopathy reported significant improvements in the treatment group following five weeks of twice daily enemas versus placebo although these differences were not sustained at 6

months after cessation of daily SCFA irrigation[161]. This latter study was conducted in patients with persistent rectal bleeding of >12 months duration after radiotherapy and it is argued that bleeding was not a result of mucosal inflammation at this stage post-treatment but more likely an artefact due to the way bleeding behaves after radiotherapy[159].

Table 1.13 Studies using SCFA interventions in pelvic radiotherapy patients

Authors & Year	Type of Study	Treatment Dose Duration	Number of Patients randomized and analysed	Treatment Setting	Reported effect of intervention
Al-Sabbagh et al[163] 1996	Intention: not stated. Open label, prospective pilot trial	SCFA enemas Daily for 4 weeks	7/7	Not available (abstract only available)	Clinical improvement in all patients. Modest but not significant change in endoscopic and pathological parameters.
Talley et al[160] 1997	Therapeutic Randomised, Double-blind cross-over trial with placebo	40ml butyric acid enema bd for two weeks	15/12	One year post radiotherapy, patients with proctopathy for >2months	No significant improvement in symptom scores during treatment versus placebo. No difference between groups in endoscopic appearance.
Pinto et al[161] 1999	Therapeutic, Randomised, Double-blind RCT with placebo	SCFA enema containing: 60mM sodium acetate 30 mM sodium propionate, 40 mM sodium butyrate acid, bd for five weeks	19/16	Post-radiotherapy, patients with chronic proctopathy for >12 months	Significant reduction in number of days of rectal bleeding in treatment group versus placebo (p=0.001) at 5 weeks. No difference in any clinical or endoscopic outcome between groups at 6 months.
Vernia et al[162] 2000	Therapeutic, Randomised Double-blind cross-over trial with placebo	80mmol/L sodium butyrate enema od for 3 weeks	20/18	Post-radiotherapy, patients with proctopathy within 3 weeks of completion of radiotherapy	Significant improvement in all clinical and endoscopic variables with treatment compared to placebo
Hille et al[164] 2008	Therapeutic (on treatment) and prophylactic in follow-up of median 50 months. Prospective cohort, open label	80mmol/L sodium butyrate enema bd for 2 weeks. Corticosteroid salvage treatment in event of non-response.	31/31	On treatment, patients with CTC Grade II proctopathy	Reduction in CTC grade II to I or 0 in 74% of patients. No correlation between efficacy of enemas in the acute setting and prevention or incidence of late toxicity.

In the most recent prospective open label study, patients on radiotherapy treatment reported reduced severity of proctopathy with butyrate enema treatment, however, there was no correlation between severity or incidence of acute toxicity and protection in the late setting[164]. A small pilot study reported non-significant improvements with use of a combined SCFA enema for 4 weeks although this report was available in abstract only and thus data are lacking[163].

The efficacy of SCFA enemas has also been explored in IBD. Four open label prospective cohort studies in patients with distal UC[165-168] have reported positive effects of SCFA enemas[165 168] butyrate enemas[166] and butyrate enemas in combination with 5-ASA[167]. Further, in five double-blind, randomised, placebo-controlled trials, two reported a significant improvement in clinical symptoms compared to placebo[169 170], one failed to find any significant differences[171] the largest (in 91 patients) reported only non-significant improvements over placebo[172] and one recent study found only minor beneficial effects on inflammatory markers following 20 days of butyrate treatment[173].

1.4.4.3 Mechanisms of action

SCFA-mediated regulation of inflammation has been extensively reviewed[174]. Butyrate has an inhibitory effect on NF-κB which plays a central role in immune and inflammatory responses[175-177]. In colonic biopsy specimens obtained from CD patients, butyrate inhibited LPS-induced activation of NF-κB through stabilisation of its inhibitor protein kappa B (I-κB) ensuring its continued sequestration in the cytoplasm and preventing translocation and transcription of pro-inflammatory cytokines TNF, IL-1 and IL-6[176]. In the same study, butyrate significantly reduced TNF levels in a dose-dependent manner in both inflamed ($p=0.0001$) and non-inflamed ($p=0.0153$) biopsies[176].

Another pre-clinical study reported that acetate, propionate and butyrate inhibited TNFα-stimulated activation of NF-κB in colo320DM cells in a dose-dependent manner and decreased LPS-stimulated TNFα release from human neutrophils[177]. Butyrate, propionate and acetate also suppressed LPS-induced production of Nitric Oxide (NO)

and cytokines TNF-α, IL-1β and IL-6 in RAW264.7 cells with enhanced production of anti-inflammatory IL-10[175]. Butyrate also potentiates the generation of anti-inflammatory Treg cells[178] [179] and protects against the accumulation of high intracellular levels of reactive oxygen species (ROS) thus inhibiting NF-κB translocation and suppressing pro-inflammatory cytokine production[180].

The G-protein coupled receptor GPR43 expressed on leukocytes, neutrophils and endothelial cells may provide a link between diet, gastrointestinal microbiota and immune and inflammatory responses[181]. Binding of SCFA to GPR43 results in activation of the MAPK signalling pathway and inhibition of histone deacetylase (HDAC) with anti-inflammatory downstream effects on gene transcription[174]. GPR43 deficient mice show exacerbated and unresolved inflammation as do germ-free mice which express little or no SCFA[181].

In addition to these anti-inflammatory actions, SCFA regulate colonic fluid balance by stimulating Na-dependent fluid absorption via a cyclic AMP-independent process involving apical membrane exchanges: Na-H, SCFA-HCO3 and Cl–SCFA[182] [183]. SCFA can also affect secretory function via inhibition of cAMP-mediated chloride secretion[133]. Animal models have shown that SCFA ion exchange mechanisms are severely perturbed during chronic ileal inflammation due to reduced transporter protein numbers[184].

The potential anti-diarrhoeal properties of SCFA have recently received attention. SCFA reduce water and electrolyte loss in cholera toxin-induced colonic secretion[185]. Oral rehydration solutions (ORS) enriched with high amylase resistant starch promote colonic SCFA production and improve ORS effectiveness by stimulating water and sodium absorption in acute diarrhoea in children [182].

The beneficial effect of butyrate in particular on colonic mucosal functions has been recently reviewed[186]. Butyrate preserves the colonic mucosal barrier through facilitation of the assembly of tight junctions and preservation of the protective

epithelial mucin layer[187] an effect that may be mediated by promotion of the expression of tight junction proteins caludin-2, and occludin[188].

The impact of butyrate on epithelial barrier function was recently explored in artificially stressed human colon-derived T84 epithelial cells. Cell monolayers were exposed to dinitrophenol which uncouples oxidative phosphorylation, and to non-pathogenic E.coli[189]. Bacterial translocation was significantly reduced by butyrate which was associated with inhibition of I-κB phosphorylation and NF-κB activation[189].

1.4.5 Summary: dietary fibre for the prevention of gastrointestinal inflammation and toxicity in patients undergoing pelvic radiotherapy for cancer

This section has explored dietary strategies that could be beneficial in patients being treated with pelvic radiotherapy with the aim of preventing or reducing radiation-induced GI toxicity. Despite a robust rationale it appears that there is a lack of data in support of increased fibre intake and its possible benefits mediated through SCFA.

Current practice in many radiotherapy departments continues to be to advise patients to reduce dietary fibre during treatment with the aim of reducing bowel frequency and optimising stool form. Local experience of the author suggests that many oncologists and dietitians are reluctant to challenge this advice in the absence of definitive data. However, patients have demonstrated that they are willing and able to follow specific dietary advice in this highly technical setting and thus do not present a barrier to fibre manipulation.

It is concluded that a sound rationale for dietary fibre manipulation during pelvic radiotherapy exists. However, evidence of the efficacy of dietary fibre in this setting appears to be lacking. Since IBD provides a model of gastrointestinal inflammation with many mechanisms and mediators that resemble those in radiation-induced GI toxicity and it is well known that nutritional strategies have been widely explored in IBD, the next step in this thesis is to gather evidence for the efficacy of dietary fibre

manipulation in IBD. If this shows anti-inflammatory benefit in IBD then it can logically be assumed that these benefits may be transferrable to radiation-induced GI toxicity.

Further, if on closer examination, it is found that there is a lack of robust data regarding the efficacy of dietary fibre manipulation in radiation-induced GI toxicity, this thesis proposes to undertake new research (a randomised controlled nutritional intervention study) to test the efficacy of dietary fibre manipulation in patients receiving radiotherapy for pelvic cancers.

1.5 Reflection and remit of this thesis

1.5.1 Reflection

Treatment-induced toxicity resulting from cancer therapy is an increasingly important issue in the current era of improved cancer survivorship. Strategies that can be employed to prevent acute severe toxicity and thus consequential late effects should continue to be explored. Nutritional strategies may be helpful. In particular, dietary fibre may offer benefit to stool type through the bulking properties of insoluble fibre and the multiple beneficial effects of SCFA, the fermentation products of soluble fibre.

IBD provides a model of gastrointestinal inflammation in which previously conducted research may provide helpful pointers for the feasibility, practicality and efficacy of a fibre nutritional intervention in patients receiving pelvic radiotherapy. A thorough evaluation of previous literature on this subject would be helpful.

The measurement of treatment-induced toxicity associated with pelvic irradiation remains complex; symptoms are a poor surrogate of underlying pathology and no gold standard markers of gastrointestinal damage have been recommended for routine use in the clinical or research setting.

The conclusion of this introduction is that evidence for the potential efficacy of dietary fibre in the management of IBD should be evaluated and that the nature of

interventional strategies employed and the results obtained should inform future research for evaluating the efficacy of similar interventions during pelvic radiotherapy.

A review of the evidence for the efficacy of fibre manipulation in patients receiving pelvic radiotherapy is essential. If, as suspected, a lack of robust evidence exists, this, coupled with positive evidence for the efficacy of fibre manipulation in the management of IBD patients, would justify the conducting of an adequately powered RCT in pelvic radiotherapy patients, powered to an appropriate symptom endpoint.

1.5.2 Research questions identified

The following research questions have been identified and merit further exploration:

- Has manipulation of dietary fibre been shown to be a useful intervention in the treatment and management of gastrointestinal inflammation in diseases such as IBD or in the prevention of radiation-induced gastrointestinal toxicity?

- Can a high fibre diet reduce or prevent the severity of acute radiation-induced gastrointestinal toxicity and symptoms during pelvic radiotherapy?

- How does dietary fibre manipulation affect the concentration or proportions of faecal SCFA during pelvic radiotherapy treatment?

- How does dietary fibre manipulation affect stool frequency, stool form, number of days with loose stool or use of anti-diarrhoeal medication during pelvic radiotherapy treatment?

- Can patients comply with high or low fibre dietary interventional advice for the duration of pelvic radiotherapy and does adherence affect body weight, body mass index (BMI), total energy intake, proportions of macronutrient intake or micronutrient intake?

1.5.3 Research hypothesis

The research hypothesis to be addressed is this thesis is as follows:

> '***Dietary fibre can prevent or reduce gastrointestinal inflammation in diseases such as inflammatory bowel disease and may be a simple cost-effective nutritional intervention to reduce or prevent acute symptoms during pelvic radiotherapy. Its mechanism of action is via production of anti-inflammatory fermentation products short chain fatty acids and through beneficial effects of dietary fibre on stool frequency and form'.***

1.5.4 Aim and scope of thesis chapters

The scope of research encompassed within this thesis addresses the hypothesis identified above, which will be answered in the following chapters:

Chapter 2: Aims

- To conduct a systematic review of the efficacy of oral (dietary) fibre interventions for the treatment or prevention of gastrointestinal inflammation in patients with IBD which represents one of the most studied and best models of gastrointestinal inflammation available and has been widely researched with respect to the efficacy of nutritional interventions.

- In the event that fibre is seen to have a positive effect in IBD, to conduct a second systematic review to establish whether any studies have been conducted assessing the efficacy of oral (dietary) fibre interventions for the treatment or prevention of radiation-induced gastrointestinal toxicity or symptoms in patients receiving radiotherapy for pelvic cancers.

- In the event that studies are identified of dietary fibre interventions in patients receiving pelvic radiotherapy, to assess whether the evidence emerging from these studies is sufficient to answer the research hypothesis outlined above (**Section 1.5.3**) and to decide if additional investigation is warranted.

Chapter 3: Aims

- If appropriate and further investigation is warranted to design an adequately powered, randomised controlled trial to investigate the efficacy of an oral dietary fibre intervention for the prevention of gastrointestinal symptoms in patients receiving radiotherapy for pelvic cancers.

- In the event that a new trial is warranted, to use the information gleaned from the two systematic reviews to inform the design of the trial, including the primary endpoint, secondary endpoints and interventional materials.

Chapters 4 and 5: Aims

- In the event that a new randomised controlled trial is conducted, to present the clinical (**Chapter 4**) and nutritional (**Chapter 5**) results of the trial with reference to the research issues identified above (**Section 1.5.2**) and to provide a critical discussion of the results, highlighting any limitations of the research conducted.

Chapter 6: Aims

- In the event that a new randomised controlled trial is conducted, to state whether the research hypothesis outlined above (**Section 1.5.3**) can be accepted or rejected and to highlight the most important findings of the trial and discuss their implications for ongoing clinical practice.

- In the event that a new randomised controlled trial is conducted, to identify fruitful areas for follow-on or additional future research.

- To reflect generally on what has been learnt in the research process and how these insights might affect ongoing clinical research in this area to ensure optimal patient care and use of research resources in the future.

CHAPTER 2: Systematic reviews

2.1 Introduction

The Introduction to this thesis has explored the inflammatory mechanisms in radiation-induced GI toxicity and IBD and found many similarities including mediators of inflammation, immunological responses, histopathology, effects on the gut microbiota and clinical symptoms. Patients with IBD and those undergoing pelvic radiation share an interest in dietary approaches to managing symptoms. Reduced incidence or severity of symptoms may occur in response to the reduction or prevention of inflammation to the gut mucosa.

Dietary fibre may be an attractive option. IBD provides an excellent model of gastrointestinal inflammation and is a disease in which the efficacy of nutritional intervention has been widely explored. Therefore, the next step in this thesis was to conduct a systematic review to gather and evaluate the evidence for the efficacy of dietary fibre manipulation in patients with IBD since it was expected that few data were available on this topic in patients receiving pelvic radiotherapy. If this review yielded promising results, a second systematic review would be indicated.

The second systematic review would aim to evaluate whether any robust evidence existed regarding dietary fibre manipulation in patients receiving pelvic radiotherapy and if so, whether the evidence enabled acceptance or rejection of the research hypothesis posed in this thesis (**Section 1.5.3**). If insufficient data was available, then the logical next step in the thesis would be to design a randomised controlled trial to test this hypothesis.

2.2 Aims

The aims of the research described in this chapter were to initially undertake a systematic review of the evidence for the efficacy of dietary fibre manipulation in the management of patients with IBD. Importantly, it was hoped that this would also inform the feasibility and nature of fibre interventional strategies that might be successfully employed in a future RCT in patients receiving pelvic radiotherapy.

Based on the results of the first review, a further systematic review would be undertaken to evaluate whether robust evidence existed for the efficacy of dietary fibre manipulation in the management of radiation-induced toxicity in patients receiving pelvic radiotherapy. If the evidence proved to be equivocal, lacking or trial designs not robust, a randomised controlled nutritional intervention trial would be recommended to test the efficacy of dietary fibre manipulation in patients receiving pelvic radiotherapy.

2.3 Methods employed in conducting systematic reviews

The methods to be employed in conducting the systematic review of the efficacy of dietary fibre in patients with IBD were agreed in advance and documented in a review protocol. In the event that a second review of the efficacy of fibre in patients receiving pelvic radiotherapy was appropriate it was agreed that the methodology employed would as far as possible be similar to ensure continuity of approach.

Both reviews would be undertaken in line with the guidelines within the Cochrane Handbook for Systematic Reviews of Interventions[190] and in accordance with the relevant criteria of the PRISMA statement (Preferred Reporting Items for Systematic reviews and Meta-Analyses)[191] and with particular reference to guidelines for the reporting of nutritional reviews[192].

2.3.1 Search strategy

Relevant studies would be identified through electronic database interrogation and hand-searching for conference abstracts. Reference lists of key publications would be screened and experts contacted for additional articles.

The electronic search strategy would be developed by the author with expert advice from a Senior Information Specialist at King's College London and in conjunction with a second researcher undertaking an MSc, also at King's College London. For electronic searching, it was agreed that limits would not be applied to ensure as wide as possible capture of all potentially relevant citations.

2.3.2 Inclusion and exclusion criteria

It was agreed that inclusion and exclusion criteria would be developed using a PICOS structure (Patient, Intervention, Comparators, Outcome, Study design) with the inclusion criteria being original randomised controlled trials reporting the effect of an oral fibre intervention (either increasing or decreasing intake) on clinical outcomes (e.g. disease, toxicity or symptom indices, disease activity or histology indices) or physiological outcomes (e.g. inflammatory markers) in adult patients (≥ 18 years).

Dietary fibre interventions eligible for inclusion would include pharmacological fibre supplements; food supplements (e.g. added cereal); or dietary advice (e.g. high fibre dietary advice) with stated focus of the intervention being dietary fibre modification.

The definition of fibre would embrace either plant cell-wall non-starch polysaccharide (NSP), which specifically excludes lignin and resistant starch[139], or the recent CODEX or European Community definitions[137 138]. Studies employing fibre-containing or fibre-free enteral formulas would not be eligible as their efficacy could relate to reasons other than the presence or absence of fibre.

Study designs would be limited to RCTs with appropriate intervention and comparator arm(s). Quality scoring would be undertaken using the JADAD scale[193].

2.3.3 Management and mediation

References would be imported into a bibliographic database (EndNote, version x5) to enable de-duplication. As far as possible, independent review (e.g. by a co-author) of the title and abstract of each reference would be undertaken prior to a final decision on eligibility. Full papers would be obtained for all potentially eligible articles and the inclusion criteria applied to each. Where papers contained insufficient information, the corresponding author would be contacted for further information. Non-English titles/abstracts would be screened by a native speaker where possible. Disagreements regarding eligibility and data extraction were to be mediated by Professor Kevin Whelan.

2.3.4 Suitability of data for meta-analysis

Suitability of data for meta-analysis would be based on degree of similarity in intervention, outcomes and patient group. Choice of the most appropriate summary statistic and model (e.g. fixed or random effect models) would depend on degree of heterogeneity of study design and the number of studies to be included within the meta-analysis. If considered appropriate, meta-analysis would be performed using Review Manager v.5 and statistical significance set at $p \leq 0.05$ where 'p' is the probability of the result being obtained under the null hypothesis.

2.4 Methods for systematic review: efficacy of fibre in IBD

2.4.1 Selection of sources and search terms

Seven electronic databases were selected and searched for relevant publications (**Table 2.1**).

Table 2.1 Electronic databases interrogated for systematic review: fibre & IBD

Online database	Years searched	Limits applied		
Inflammatory Bowel Disease		***Adults***	***Study design***	***Humans***
MEDLINE	1956 - October 2012	*No*	*No*	*No*
EMBASE	1947 - December 2012	*No*	*No*	*No*
CINAHL (Nursing database)	1983 - 2012	*No*	*No*	*No*
Cochrane CENTRAL library	All years available	*No*	*No*	*No*
CAB Direct (Nutrition)	All years available	*No*	*No*	*No*
Web of Science	1900 - December 2012	*No*	*No*	*No*
Scopus	1996 – December 2012	*No*	*No*	*No*

Search terms and syntax differed for each database (**Table 2.2**).

Table 2.2 Search terms for electronic databases: fibre & IBD

Medline and Embase

1. (((Dietary adj1 Fibre) or Dietary) adj1 Fib*).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
2. Dietary Fibre/
3. (Non-starch polysaccharide or NSP).mp [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
4. Cellulose.mp. or Cellulose/
5. Methylcellolose.mp. or Methylcellulose/
6. Cereals/ or Cereal*.mp.
7. (Residue adj1 Diet).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
8>.Roughage.mp.
9.(Bran or (Oat and Diet)).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
10. Psyllium.mp. or Psyllium/
11. Plantago/ or Plantago*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
12. (Ispaghula* or ispaghulahusk).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
13. Pectin.mp. or pectins/
14. Guar gum.mp.
15.Prebiotics.mp. or prebiotics/
16. (Prebiotoc* or Synbioitc).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
17. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
18. exp Inflammatory Bowel Diseases/ or Inflammatory bowel disease*.mp.
19. IBD.mp.
20. Intestinal inflammation.mp.
21. Crohn Disease/ or Crohn* disease.mp.
22. (Ulcerative colitis or UC).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
23. Pouchitis.mp. or pouchitis/
24. 18 or 20 or 21 or 22 or 23
25. 17 and 24

CINAHL

http://search.ebscohost.com/login.aspx?direct=true&db=cin20&bquery=((((((%22Dietary+Fibre%22)+or+(MH+22Dietary+Fibre%22)))+OR+((%22Non+starch+polysaccharide+OR+NSP%22))+OR+(((%22cellulose%22)+OR+(MH+%22Cellulose%22)))+OR+(methylcellulose)+OR+(522roughage%22)+OR+((%22Bran+OR+Oat%22))+OR+(((%22Psyllium%22)+OR+(MH+%22Psyllium%22)))+OR+(Plantago*)+OR+((%22Gum%22))+OR+(((%22Prebiotics%22)+OR+(MH%22Prebiotics%22)))+OR+((%22Prebiotic*+or+Synbiotic%22))+AND+((((%22Inflammatory+bowel+disease%22)+OR+(MH+%22Inlammatory+bowel+diseases%2b%22)))+OR+(IBD)+OR+((%22Intestinal+inflammation%22)+OR+((%22Crohn's+disease%22))+OR+((%22Ulcerative+colitis%22)+OR+(UC)+OR+(((%22Pouchitis%22)+(MH+%22Pouchitis%22))))))&type=1&site=ehost-live

CENTRAL (Cochrane Database)

#1(Dietary Fibre OR Dietary Fibre OR Non starch polysaccharide OR NSP OR cellulose OR methylcellulose OR cereal* OR "Residue Diet" OR Roughage OR Bran OR Oat AND Diet OR Psyllium OR Plantago* OR ispaghula* OR Pectin OR Guar gum OR Prebiotic OR Synbiotic) and (Inflammatory Bowel Disease OR IBD OR "Intestinal Inflammation" OR "Crohn* Disease" OR Ulcerative Colitis OR UC OR Pouchitis)

Table 2.2 Search Terms for electronic databases: fibre & IBD

CAB Direct: Fibre & IBD

(Dietary Fibre OR Non Starch Polysaccharide OR NSP) OR (Cellulose OR Methylcellulose OR Cereal OR Residue Diet OR Roughage OR Bran OR Oat OR Psyllium OR Plantago OR Ispaghula OR Pectin OR Guar gum OR Prebiotic OR Synbiotic) AND (Inflammatory Bowel Disease OR IBD OR Intestinal Inflammation OR Crohn's Disease OR Ulcerative Colitis OR UC OR Pouchitis)

Web of Science: Fibre & IBD

#1: TS=("Dietary Fibre" OR 2Dietary Fibre" OR "Dietary Fib*"OR Non starch polysachharide OR NSP OR Cellulose OR Methylcelluloe OR Cereal* OR "Residue Diet" OR Roughage OR Bran OR Oat AND Diet OR Psyllium OR Plantago* OR Ispaghula OR Pectin OR Guar gum OR Prebiotic OR Synbiotic) #2: TS=(Inflammatory Bowel Disease OR IBD OR "Intestinal Inflammation" OR "Crohn* Disease" OR Ulcerative Colitis OR UC OR Pouchitis) #3: #1 AND #2

SCOPUS: Fibre & IBD

(((“Dietary Fibre” OR “Dietary Fibre” OR “Dietary Fib*”OR Non starch polysaccharide OR NSP OR cellulose OR methylcellulose OR cereal* OR “Residue Diet” OR Roughage OR Bran OR Oat AND Diet OR Psyllium OR Plantago* OR ispaghula* OR Pectin OR Guar gum OR Prebiotic OR Synbiotic) AND ((Inflammatory Bowel Disease OR IBD OR “Intestinal Inflammation” OR “Crohn* Disease” OR Ulcerative Colitis OR UC OR Pouchitis)))

Hand searching to identify non-electronically indexed items spanned the period 2001-2013 (**Table 2.3**).

Table 2.3 Hand searching sources: fibre & IBD

Organisation / Event	Relevant publication(s)
Digestive Diseases Week	Gastroenterology
British Society of Gastroenterology	Gut
American Society for Parental and Enteral Nutrition	Journal of Parenteral and Enteral Nutrition
European Society for Clinical Nutrition & Metabolism	Clinical Nutrition, Clinical Nutrition Supp, e-SPEN
British Dietetic Association	Journal of Human Nutrition and Dietetics
British Association for Parenteral & Enteral Nutrition	Proceedings of the Nutrition Society

2.4.2 Inclusion and exclusion criteria

Inclusion and exclusion criteria were defined according to the PICOS structure and are detailed in **Table 2.4**

Table 2.4 Inclusion and exclusion criteria: fibre & IBD

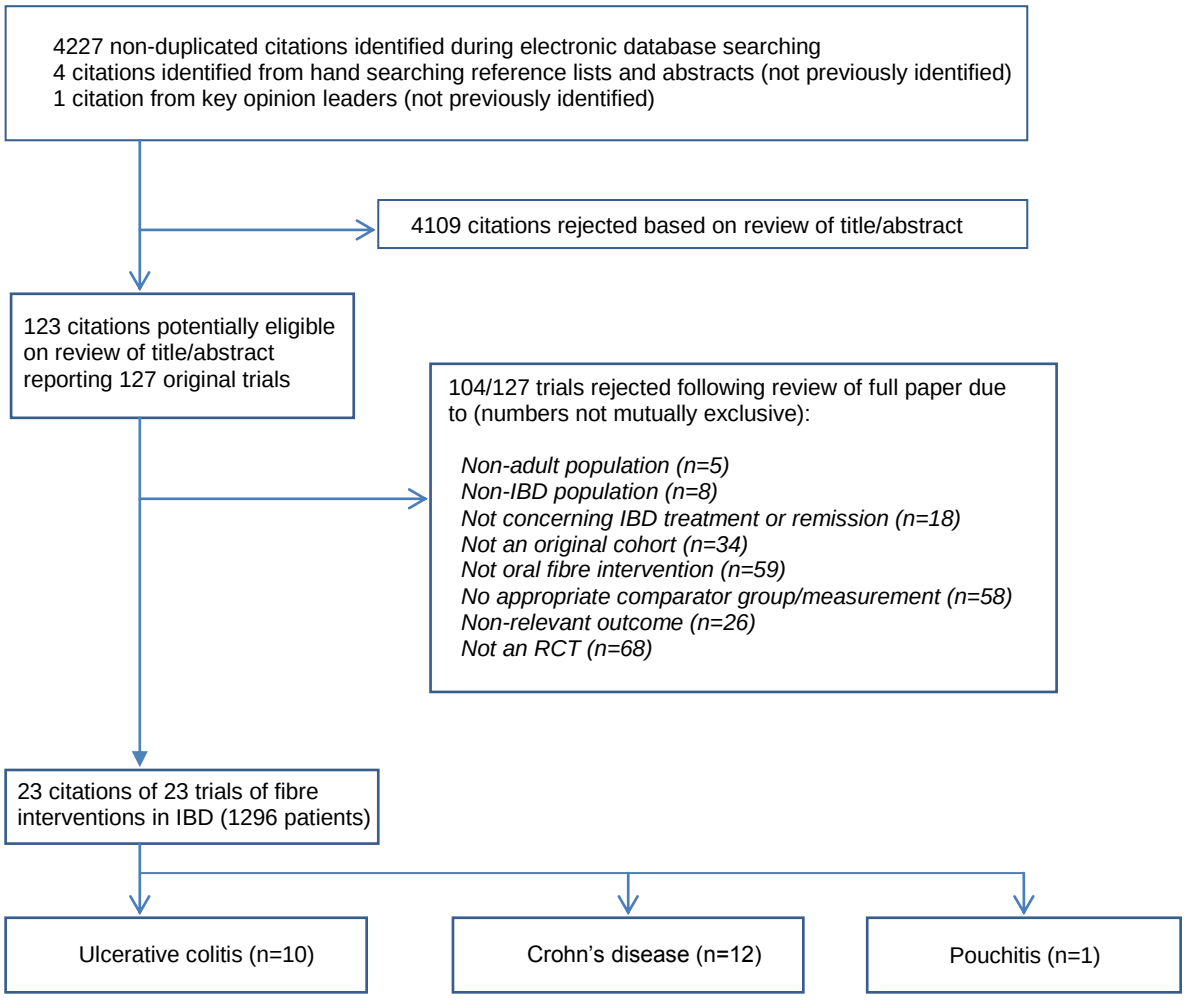
PICOS	Inclusion and exclusion criteria	Data extracted
Patient	Adult (in- or out-patients) over 18 y with Crohn's disease, UC or pouchitis in remission or relapse. Original cohorts only (i.e. excluding previous reports and abstracts of the same patients) to avoid duplication of patient numbers.	Location, clinical setting, age, gender, number of patients recruited, number of patients evaluated (i.e. those with evaluable data at study end). Disease type, disease stage and /or disease severity
Intervention	Oral pharmacological fibre supplement, food supplement or dietary advice to increase or decrease fibre intake were eligible. Fibre interventions were required to meet the acknowledged definitions of fibre (15-17), and therefore included prebiotic fibres. Synbiotic preparations containing a named prebiotic fibre complying with the cited fibre definitions were also eligible irrespective of probiotic species and strain(s) used.	Fibre source, dose, presentation and period of administration. Presence of co-administered 'standard' medication(s) or supplemental nutritional substances. Compliance with interventional dose (if reported) and method of computing compliance. Genus/species/strain of probiotic if administered in conjunction with synbiotic preparation.
Comparators	Reports including a comparator group of either a placebo, no dietary intervention, an alternative dietary intervention or a pharmacological intervention were included. Reports comparing doses of fibre without any other comparator group were excluded.	Patient numbers in the intervention and comparator groups and nature of intervention. Group names standardised to avoid confusion
Outcomes	Clinical outcomes or endpoints including remission, relapse, mortality, morbidity, medication use, symptoms, Quality of Life. Physiological outcomes or endpoints related to gastrointestinal inflammation including histology, inflammatory and immunological markers, microbiota and metabolic substrates. Presence or absence of adverse events related to interventional substrate.	Values, scores or counts for remission rates, remission duration, response rates, disease activity (measured using standardised indices), mortality, morbidity, medication use, symptoms, Quality of Life. Otherwise all other relevant clinical or physiological outcomes or endpoints at relevant time-points including statistical significance if reported. Comparisons of endpoint data between groups were extracted where possible, but within group comparisons between baseline and follow-up were extracted where of interest.
Study design	Randomised controlled trials (RCT). Open label, wholly or partially blinded or placebo-controlled nutritional interventional studies were eligible. Single or multi-centre. English or foreign language. Non-RCTs and uncontrolled trials were excluded.	Type of study design, nature of blinding, active interventional period and duration of follow-up. Authors and publication details. Abstract or full report. Language of publication.

2.5 Results of systematic review: efficacy of fibre in IBD

2.5.1 Results of the search process

A total of 4232 non-duplicated papers were identified. Titles and abstracts of each were reviewed and 123 papers were potentially eligible. Following full review, 23 papers (detailing 23 eligible studies) fulfilled the inclusion criteria (**Figure 2.1**).

Figure 2.1 Fibre & IBD: Summary of review process and results



Ten studies were in patients with UC[194-203] of which one was published as an abstract only[196]; 12 were in CD[204-215], of which two were non-English language[210 215], two were abstracts[205 212] and one a letter[213]; and one was in pouchitis[216]. Of the 17 experts contacted, 71% responded and one additional study was identified.

2.5.2 Patients, interventions and comparators

The 23 studies comprised 1296 recruited patients of which 35% were male (where reported). This included 447 patients with UC (46% in remission; 26% with active disease; 28% with 'mixed' disease activity), 829 with CD (56% remission; 23% active; 21% 'mixed') and 20 with pouchitis, all in remission. The methods used to classify patients as in remission or not varied between and within diseases. Where employed (16/23 studies) nine different named disease indices were used (5 different indices in UC; 4 in CD; one in pouchitis) and one study (in UC) used a bespoke symptom questionnaire. Use of concomitant medications was reported in 20/23 studies and included 5-ASA, 6MP, steroids, anti-TNF-α antibody or none.

Fibre supplements were used in seventeen[194-205 208 210 213 216] studies and dietary interventions were used in six[206 207 211 212 214 215]. Most investigated the efficacy of increased fibre intake, except for one dietary intervention that investigated a low fibre diet[211]. Double blinding occurred in ten studies[196 198-200 204 205 208 209 213 216] and blinding of some or all researchers in an additional seven studies[201 203 206 207 211 214 215]. Most studies compared fibre to no intervention or placebo.

The majority (10/17) of fibre supplement studies were compared with placebo[195 198-200 204 205 208 209 213 216], whereas most high fibre dietary interventions were compared with other dietary interventions (e.g. low fibre) and none were compared with a 'sham diet'. In the fibre supplement studies, intervention periods ranged from 2-w to 24-m. All supplements were soluble fibres (e.g. germinated barley, inulin, oligosaccharide/inulin mix, psyllium) in doses ranging from 5-30 g/d. Seven studies also used probiotics alongside the fibre supplement[198 199 202-205 208]. In the supplement

studies, some reported compliance, commonly based on counts of unused sachets, however, none quantified fibre intake from background diet.

Of the dietary interventions, the duration ranged from 28-d to 24-m resulting in intakes of between 13-46 g/d of fibre (where reported), although none reported the relative contributions of insoluble and soluble fibres. Monitoring of dietary compliance varied and included monthly, quarterly, 6-monthly and *ad-hoc* reviews using a variety of methods to estimate fibre intake (e.g. food diary, 24-hour recalls).

2.5.3 Study quality and adverse events

Serious adverse events were inconsistently reported and where reported were unrelated to intervention. No studies were terminated on safety grounds. Most studies clearly reported patient withdrawals (19/23). Few studies were of high quality, with only 17% (4/23) scoring the maximum 5 points, 26% (6/23) 4 points, 22% (5/23) 3 points, 17% (4/23) 2 points and 17% (4/23) 1 point on the JADAD score (**Tables 2.5, 2.6, 2.7**).

2.5.4 Clinical and physiological outcomes

2.5.4.1 Fibre and Ulcerative colitis (remission)

Four studies in UC patients in remission recruited 213 patients. In a large 3-arm open label RCT, comparing psyllium fibre *versus* mesalamine *versus* mesalamine and psyllium fibre[194], continued remission at 12-m was similar across all groups, implying equivalence between fibre and medication (although it was not powered for an equivalence endpoint) and lower relapse rates in the mesalamine and psyllium fibre group[194]. A further small RCT (n=31) showed lower treatment failure rates due to relapse at 12-m for psyllium fibre and mesalamine *versus* mesalamine alone[196].

In a double-blind cross-over RCT, although disease activity (remission, relapse) were not measured, patients consuming psyllium fibre reported lower global symptom scores and total number of symptoms at 2-m compared with placebo[195]. In a recent open label study, disease outcomes were not reported with no difference in blood

markers Tumour Necrosis Factor-α (TNF-α), interleukin-6 (IL-6) and interleukin-8 (IL-8) between supplemented and non-supplemented groups at 2-m[197].

2.5.4.2 Fibre and Ulcerative Colitis (active disease or mixed active/remission)

Five studies in UC patients with active disease[198-202] recruited 114 patients, although four of these studies[198-201] each recruited ≤20. In one double-blind RCT, there were no differences in the numbers achieving remission after two weeks between patients receiving prebiotic fibres (oligofructose/inulin) or placebo[200]. Those receiving prebiotic fibres had significantly lower fecal calprotectin compared to placebo on day 7 but not on day 14, and lower values on day 7 and 14 compared to baseline[200]. However, there were no differences between groups in the change in inflammatory markers such as IL-6 and prostaglandin-2 (PGE-2)[200].

The same prebiotic fibre was used in a double-blind RCT in combination with a probiotic (synbiotic)[199]. The synbiotic did not result in significantly lower disease activity and sigmoidoscopy scores compared with placebo, although there was lower TNFα and IL-1α expression. Compared to baseline values, the synbiotic increased luminal *bifidobacteria*-specific total rRNA and a reduction in epithelial immunological markers (e.g. human β-defensins) compared to baseline values, indicating a reduced inflammatory profile[199].

A small open-label RCT using 20-30 g/d of germinated barley fibre resulted in lower disease activity compared with no intervention at one month but no change in physiological markers of disease activity[201]. A double-blind RCT of prebiotic fibre (oligosaccharides/inulin) with added glutamine found no differences in clinical variables (e.g. rectal bleeding, bowel frequency) compared with placebo or baseline, but at 2-m there was reduced expression of pro-inflammatory IL-6 and IL-8 compared to baseline, but not to placebo[198]. The largest (n=41) and most recent open label study reported no clinical benefit of a synbiotic supplement comprising 5 g/d galacto-oligosaccharide plus probiotic at 1-y. However, significantly reduced expression of inflammatory marker myeloperoxidase was reported between the synbiotic and non-intervention groups[202].

One open-label RCT (n=120) in a mixed UC cohort (remission and mildly active) comparing psyllium fibre *versus* probiotic *versus* psyllium fibre/probiotic did not find differences in endpoints between the groups, although an increase in total IBDQ score (improvement in symptoms) and reduction in C-reactive protein occurred at one month in the psyllium fibre/probiotic group[203].

2.5.4.3 Fibre and Crohn's disease (remission)

Four studies in CD patients in remission have recruited 465 patients. Two studies investigated a combined high fibre, low sugar diet[206 207]. In one, twenty patients with parenteral- or enteral-induced remission had their standard medication ceased. Patients randomised to the high fibre diet experienced significantly higher treatment failure and shorter time to relapse (1.4 versus 2.8 m) compared with patients on a low fibre exclusion diet[206]. The other study, recruited 352 patients with inactive disease and found no differences in the number of patients with deteriorating disease at 24 m between the high fibre (mean intake 27 g/d) and low fibre (mean intake 15 g/d) groups although any effect of concomitant low sugar consumption in the high fibre group was not adjusted for[207].

Two RCTs investigated the efficacy of a fibre and prebiotic supplement in combination with probiotics compared with placebo to maintain remission[204 205]. One aimed to prevent post-operative disease recurrence[204] and the other aimed to prolong the time between 'rescue' anti-TNF-α infusions[205]. There were no differences between intervention and placebo groups in clinical, endoscopic or physiological outcomes at 24-m[204] or median time to next infusion at 6-m[205].

2.5.4.4 Fibre and Crohn's disease (active disease or mixed active/remission)

Five studies in CD patients with active disease recruited 193 patients, two of which used a dietary intervention[211 212]. One study compared a high fibre diet (mean intake 46 g/d), rich in organic foods, with a low fibre (16 g/d), non-organic diet and reported a similar proportion of patients achieving remission[211]. Although those in the high fibre group had improved endoscopic appearance and bowel sonography scores after 6-w,

numbers were small and no other differences in physiological or clinical outcomes were observed. A further open label study (n=7) reported significantly improved IBDQ scores following a 28-d high fibre low refined carbohydrate diet compared to those in the non-intervention group, but disease activity was not measured *per se* [212].

Of the three studies using fibre supplements, one open-label RCT did not record the impact on disease activity specifically, although it did report that patients taking psyllium fibre for 3-m had significantly improved stool consistency and slower gut transit times compared with controls[210]. Two recent double-blind RCTs using 12-15 g/d of prebiotic fibre (oligofructose/inulin), one in combination with probiotic[208], have returned mixed results[208 209].

In the smaller, long term study, only 24 patients were available for follow-up at 6-m, at which point there were no statistically significant differences in remission rates between groups[208]. Patients in the fibre group had reductions in histological and disease activity scores at 6-m and increases in bifidobacteria, however, these effects were in comparison with baseline values rather than with the placebo group. In the larger RCT there was no difference between groups in clinical endpoints (disease activity, numbers achieving response or remission), fecal calprotectin or selected microbiota at one month[209], indeed, significantly more patients withdrew in the prebiotic fibre group due to increased gastrointestinal symptoms including flatulence, borborygmi and abdominal pain. However, there were indications of a shift to greater mucosal immunoregulation in the prebiotic fibre group including significantly higher IL-10 and lower IL-6 positive dendritic cells[209].

Three RCTs in mixed patient cohorts (i.e. active disease/remission) recruited 171 patients. One used a high fibre diet compared with an exclusion diet and found no difference between groups in clinical or physiological outcomes at one year[215]. One study investigated a fibre-restricted diet (mean intake 3 g/d) and found no difference in clinical outcomes at 29-m compared with patients consuming their habitual diet (mean intake 13 g/d)[214]. A recent study reported that prebiotic fibre (oligofructose/ inulin) resulted in no difference in disease activity compared to placebo at 4-w,

although there were improvements compared with baseline values[213], alongside significant increases in *Bifidobacteria longum* in the prebiotic fibre group.

2.5.4.5 Fibre and Pouchitis

A single cross-over RCT of 20 patients with pouchitis in remission investigated an oral nutritional supplement (consumed in conjunction with normal diet) with or without an additional prebiotic fibre (inulin) supplement for 3-w[216]. Favourable outcomes were reported during fibre supplementation including significantly lower disease activity and higher butyrate concentration compared to placebo. There were no differences in *bifidobacteria* and *lactobacilli*, however, there was a reduction in *Bacteroides fragilis*, some strains of which are enterotoxigenic and induce colitis[217].

In summary, fibre supplementation had a positive effect on disease outcomes in 3/10 studies in UC[194 196 201] and in the sole pouchitis study[216]. In contrast, none of the 12 studies in CD showed a benefit with 5/12 studies reporting no effect on disease outcomes[204 205 208 209 213] and 3/12 equivalence[207 211 215](**Table 2.8)**.

Table 2.5 Randomised controlled trials of fibre interventions in adult patients with ulcerative colitis

Reference	Patient details	Study details			Intervention		Outcomes
	Disease *N recruited* *N evaluated* *Male : Female* *Age (mean)*	*Design*	*Jadad*	*Groups*	*Details by group*	*Duration*	*Clinical and physiological outcomes:* *between and within groups*
Fernandez-Banares et al 1999[194]	Remission UC 105 recruited 102 evaluated 55 M : 47 F 43 yrs	Open label	3	G1: Mesalamine (1.5g/day) G2: Fibre G3: Fibre + mesalamine	G1: No additional fibre G2: Psyllium (20g/d) G3: P syllium (20g/d)	12-m	*Clinical:* No difference between groups in probability of continued remission (*p=0.67*) No difference between groups in treatment effects after adjusting for confounding variables (*p=0.41*) Lower relapse rates in G3 (23.3%) compared to G1 (37.1%) and G2 (35.1%) *Physiology:* Raised fecal butyrate in G2patients at 3 months compared to baseline values (*p=0.018*) (n=7)
Hallert et al 1991[195]	Remission UC 36 recruited 29 evaluated 14 M : 22 F 43 yrs	Cross-over Double blind Placebo	4	G1: Placebo (standard meds) G2: Fibre (standard meds)	G1: Placebo G2: Psyllium (7g/d)	2-m per group	*Clinical*: Reduced severity of total gastrointestinal symptoms in G2 versus G1 (*p<0.001*) Reduced total number of symptoms in G2 versus G1 (*p<0.001*)
Copachi et al 2000[196]	Remission UC 31 recruited 31 evaluated Gender NR Age NR	Open label	1	G1: Mesalamine G2: Fibre + mesalamine G3: Probiotic + mesalamine	G1: No additional fibre G2: Psyllium (dose NR) G3: No additional fibre, *S.boulardi*	12-m	*Clinical:* Reduced treatment failure rate (relapse) in G2 (28%) versus G1 (35%) (*p=0.02*) and G2 versus G3 (30%) (*p=0.05*) No difference between groups in probability of continued remission (*p=NR*) Increased number of asymptomatic nights in G2 versus G1 and G3 (*p=0.001*)
Faghfoori et al 2011[197]	Remission UC 41 recruited 41 evaluated 26 M : 25 F 33.5 y	Open label	1	G1: Control (standard meds) G2: Fibre supplement (standard meds)	G1: no supplement G2 Germinated barley (30 g/d)	2 m	*Physiology:* No differences in TNF-a, Il-6, IL-8 between G1 and G2 at 2 m, although significant reduction in these in G2 between baseline and 2 m.
Federico 2009[198]	Active UC 18 recruited	Double blind Placebo	4	G1: Placebo (standard meds) G2: Prebiotic fibre/probiotic (standard meds)	G1: Placebo (starch) G2: Oligosaccharide/inulin (7 g/d), plus *L. paracasei* ($5x10^9$cfu),	2-m	*Physiology:* Lower serum IL-6 (*p<0.05*) and IL-8 (*p<0.01*) in G2 at 2m compared to baseline values.

	16 evaluated 9 M : 9 F 47 yrs				plus added micronutrients		Lower lymphocytic expression of IL-8 (*p<0.01*) in G2 at 2m compared to baseline value.
Furrie 2005[199]	Active UC 18 recruited 14 evaluated 8 M : 8 F 41.5yrs	Double blind Placebo	5	G1: Placebo (standard meds) G2: Prebiotic fibre/probiotic (standard meds)	G1: Placebo (starch, maltodextrose) G2: Oligofructose/inulin (12 g/d), plus *B. longum* ($2x10^{11}$cfu)	1-m	*Clinical:* Reduced sigmoidoscopy scores in G2 versus G1 (*p=0.06*) No difference between groups in mean clinical disease activity score Bowel frequency improved in G2 versus G1 at 1 m (p=NR) *Physiology:* Reduced expression of TNFα and IL-1α in G2 at 1m compared to G1 (*p=0.0177 and 0.0051 respectively)* No difference between groups at 1 m in the expression of immunological markers, human beta defensins (hBD2,3 & 4) Lower hBD2, 3 and 4 in G2 at 1m compared to baseline values (*p=0.016, 0.038 and 0.008*) Raised (42-fold increase) in bifidobacterial specific total rRNA in G2 at 1m compared to G1 (4.6-fold increase)
Casellas 2007[200]	Active UC 19 recruited 15 evaluated 6 M : 13 F 36.5yrs	Double blind Placebo	4	G1: Placebo (standard meds) G2: Prebiotic fibre (standard meds)	G1: Placebo (maltodextrin) G2: Oligofructose/inulin (12 g/d)	14 d	*Clinical:* No difference between groups in change in disease activity scores. All patients in G2 in clinical remission at 14 days (7/7) compared to 75% (6/8) patients in G1 (p=0.155). Lower disease activity scores in both groups compared to baseline (*p<0.05*) *Physiology:* Reduced fecal calprotectin in G2 versus G1 at 7 days (*p<0.05*) but not at 14 days Lower fecal calprotectin in G2 at 7 and 14 days compared to baseline values (*p<0.05*) No difference between groups in change in inflammatory mediators (IL-6 and PGE-2) or fecal DNA
Kanauchi 2002[201]	Active UC 18 recruited 18 evaluated Gender NR 37.05yrs	Open label	3	G1: Control (standard meds) G2: Fibre (standard meds)	G1: No additional fibre G2: Germinated barley (20-30 g/d)	1 m	*Clinical:* Reduced disease activity score in G2 versus G1 at 1 m (*p=0.045*) *Physiology:* No difference between groups in the change in serum C-reactive protein concentrations between baseline and 1 m
Ishikawa et al 2011[202]	Active UC 41 recruited 39 evaluated	Open label	2	G1: Control (standard meds) G2: Probiotic, prebiotic fibre (standard meds)	G1: no supplement G2: *B. breve* ($3x9^{9}$cfu), Galact-oligosaccharides (5 g/d	I yr	*Clinical:* No difference in endoscopic score between G1 and G2, but lower scores between baseline and 1 y in G2 *Physiology:*

	24 M : 17 F 45.5 yrs						Lower myeloperoxidase at 1 y in G2 compared with G1 ($p<0.05$)
Fujimori et al 2009[203]	Mixed UC (remission, mildly active) 120 recruited 94 evaluated 39 M : 55 F 36 yrs	Open label	3	G1: Probiotic (standard meds) G2: Fibre (standard meds) G3: Probiotic, Fibre (standard meds)	G1: *B. longum* ($2x9^9$cfu) G2: Psyllium (8g/d) G3: Psyllium, B.longum	1 m	*Clinical*: Improved IBDQ scores at 1 m in G3 (*p=0.03*) but not in G1 or G2 compared to baseline value *Physiology:* Decrease in C-reactive protein in G3 at 1m (*p<0.05*) compared to baseline value

Table 2.6 Randomised controlled trials of fibre interventions in adult patients with Crohn's disease

Reference	Patient details	Study details			Intervention details		Outcomes
	Disease ***N recruited*** ***N evaluated*** ***Male : Female***	***Design***	***Jadad***	***Groups***	***Details by group***	***Duration***	***Clinical and physiological outcomes:*** ***between and within groups***
Chermesh et al 2007[204]	Remission CD 30 recruited 9 evaluated 23 M : 7 F 35.7 yrs	Double blind Placebo	5	G1: Placebo (standard meds) G2: Prebiotic fibre/probiotic (standard meds)	G1: Placebo G2: β-glucans (2.5g), inulin (2.5g), pectin (2.5g), resistant starch (2.5g), plus 4 probiotic species	24-m	*Clinical:* No difference between groups in rate of clinical relapse or weight, frequency of bowel movements or abdominal pain score at any time points *Physiology:* No significant difference between groups in endoscopy score at 3 months (n=21) or 24 months (n=8) post-surgery No difference between groups in CRP, albumin, ESR or urea and electrolytes at any time points
Rutgeerts 2004[205]	Remission CD 63 recruited 38 evaluated M : F NR Age NR	Double blind Placebo	4	G1: Placebo G2: Prebiotic fibre/probiotic Use of standard meds (excluding Infliximab) : NR	G1: Placebo G2: β-glucans, inulin, pectin, resistant starch (total 10 g/d), plus lactobacilli ($4x10^{10}$ cfu)	6-m	*Clinical:* No difference between groups in time between baseline and next ('rescue') infliximab infusion (G2: 9.79 weeks) versus (G1: 10.14 weeks) No difference between groups in median interval between Infliximab infusions (G2 -2.83 weeks) versus G1 (+1.24 weeks) No difference in time to relapse G2 (9.79 weeks) v G1 (10.14 weeks) following baseline Infliximab infusion (p=0.51)
Jones et al 1985[206]	Remission CD 20 recruited 20 evaluated 2 M : 18 F Age 20-29 yrs (mode)	Open label	2	G1: Exclusion diet and stepwise reintroduction (cessation of meds) G2: Unrefined carbohydrate, fibre-rich (cessation of meds)	G1: Exclusion dietary advice G2: UCFR dietary advice	6-m	*Clinical:* Higher treatment failure rate in G2 (n=8 relapsed within 2 months and all within 6 months) versus G1 (n=7 in remission at 6months) ($p<0.05$). Reduced mean time to relapse in G2 (1.38 months) versus G1 (2.75 months) *Physiology:* Improved erythrocyte sedimentation rate and orosomucoid concentration in G1 patients in remission at 3 and 6 months compared to baseline
Ritchie et al 1987[207]	Remission CD 352 recruited 102 evaluated	Open label	3	G1: Low fibre, *ad libitum* sugar (standard meds) G2: High fibre, restricted sugar (standard meds)	G1: Low fibre advice (c. 16 g/d) G2: High fibre advice (c. 27 g/d)	24-m	*Clinical:* No difference between groups at 24 months in the proportion of patients remaining in remission (G1: 64% relapse free) versus (G2: 59% relapse free)

	130 M : 222 F Age 35 yrs						No difference between groups in the change in disease activity score, stool frequency or body weight in patients who remained in the study at 24 months.
Steed et al 2010[208]	Active CD 35 recruited 24 evaluated 13 M :11 F Age 48 yrs	Double blind Placebo	5	G1: Placebo (standard meds) G2: Prebiotic fibre/probiotic (standard meds)	G1: Placebo G2: Inulin/oligofructose (12g/d), plus B. longum ($2x10^{11}$ cfu)	6-m	*Clinical:* Fall in CDAI disease activity score in G2 of 72 points (*p=0.020*) compared to baseline. Eight of 13 patients (62%) in remission at 6 months in G2 compared to five of 11 patients (45%) in G1 (*p=0.431)* No significant improvements in either group at 6 months compared to baseline values for stool volume or consistency or IBDQ score *Physiology*: Reduced (i.e. improved) histological score in G2 at 6 months compared to baseline value of 3 points (p=0.018) Reduced TNF-α expression in G2 at 3months (*p=0.041*) compared to baseline value but reduction not significant at 6 months No difference at 6 months compared to baseline values in either group in mucosal expression of IL-18, INF-γ, IL-1β or blood marker CRP Increased bifidobacteria in G2 at 6months compared to baseline values (*p=0.0259*)
Benjamin et al 2011[209]	Active CD 103 recruited 103 evaluated 40 M : 63 F Age 39.5 yrs	Double blind placebo	5	G1: Placebo (standard meds) G2: Prebiotic fibre (standard meds)	G1: Placebo (maltodextrin) G2: Inulin/oligofructose (15g/d)	1-m	*Clinical:* No significant difference between groups in proportion of patients achieving clinical response (G1: 22% versus G2: 39%) (*p=0.067*) No significant difference between groups in proportion of patients achieving remission (G1: 11% versus G2: 20%) (*p=0.193*) No significant difference between groups in mean disease activity scores at 1 month (G1:250 points versus G2: 220 points) (*p=0.112*) Significantly worse IBDQ scores in G2 at 1 month G2: 129.9 points versus G1: 149.8 points) (*p=0.004*) Significantly greater proportion of patients withdrawn in G2 (G2: 26% versus G1: 8%) (*p=0.0018*) *Physiology:* No significant difference between groups at 1 month in faecal calprotectin but reduced increase in G2 at 1 month (*p=ns*) compared to baseline value Significant increase in dendritic cell IL-10 in G2 (*p=0.035*) compared to baseline value Significant reduction in proportion of IL-6 positive dendritic cells at 1 month in G2 (*p=0.036*) compared to baseline value No significant difference between groups in faecal concentrations of

							bifidobacteria or f. prausnitzii at 1 month
Koch 1984[210]	Active CD 30 recruited Evaluated: NR 12 M : 18 F Age: 17-51 yrs	Open label	3	G1: Standard meds G2: Fibre (standard meds)	G1: No intervention G2: Isphagula (10 g/d)	3-m	*Clinical:* Improved stool consistency in G2 versus G1 (*p<0.05*) Slower stool transit in G2 v G1 (*p<0.01*)
Bartel et al 2008[211]	Active CD 18 recruited 14 evaluated 9 M : 5 F	Open label	2	G1: Low fibre (standard meds) G2: High fibre (standard meds)	G1: Active phase: Low fibre advice (mean16g/d fibre) comprising: Low fibre, avoid fruit and vegetables, low fat, high carbohydrate, no red meat. Follow-up phase: avoid fibre-rich fruit and vegetables, include red meat G2: Active phase: Active diet. High fibre advice (mean 46 g/d) comprising: spelt bread, red meat organically farmed, no fruit and vegetables. Follow-up phase: Include fruit and vegetables, dairy items, avoid processed foods and refined sugar	6-w (active) 18 week (follow-up)	*Clinical:* No difference between groups at 6 weeks in improvement in disease activity indices (IBDQ and CDAI) No difference between groups at 6 weeks in the proportion of patients in remission G1 (78%) versus G2 (80%) No significant differences between groups in clinical outcomes reported after 24 weeks follow-up *Physiology:* Improved mucosal appearance in G2 (3 of 4 patients) at 6 weeks versus G1 (1 of 9 patients) (*p=0.027*) No difference between groups at 6 weeks in blood markers of inflammation or nutritional status including ESR, CRP, protein, albumin, transferrin and ferritin Bowel sonography (TABS) score improved in 80% of G2 patients versus 12.5 % of G1 patients at 6 weeks (*p=0.016*)
Brotherton et al 2012[212]	Active CD 7 recruited 7 evaluated M : F NR	Open label	1	G1: Control group G2: Unrefined carbohydrate, fibre-rich	G1: "General diet advice" (dose: NR) G2: Wheat bran (0.5 cup/d), low refined carbohydrate advice	28 d	*Clinical:* Higher QoL score in G2 compared with G1 at 28 d
Joossens et al 2012[213]	Mixed CD (active CD and CD in Remission) 67 recruited 40 evaluated M : F NR	Double blind placebo	4	G1: Placebo (standard meds) G2: Prebiotic fibre (standard meds)	G1: Placebo G2: Inulin/oligofructose (20g/d)	1-m	*Clinical:* Greater proportion of patients withdrew in G2 versus G1 due to side effects (*p=0.07*) Significant decrease in disease activity in patients with active disease in G2 (n=8) compared to baseline score (p=0.029) *Physiology:* Significant increase in number of *B. longum* in G2 at I month (p=0.03) compared to baseline

							No change in either group in levels of *F. prausnitzii* at 1 month compared to baseline
Levenstein et al 1985[214]	Mixed CD (active CD and CD in Remission) 71 recruited 58 evaluated 36 M : 35 F	Open label Single blind (Clinician)	2	G1: Normal diet G2: Low fibre diet	G1: Habitual fibre (13 g/d) G2: Low fibre (3g/d)	29-m	*Clinical:* No difference between groups in mean 'in-study' disease activity score (G1: 33.1 versus G2: 33.7) using New CDAI (NCDAI) No difference between groups in requirement for surgery (14.3% requiring intervention in G1 versus 16.7% in G2) No difference between groups in change in weight between 1 and 29 months
Stange et al 1990[215]	Mixed CD (active CD and CD in Remission) 33 recruited 28 evaluated 12 M : 16 F	Open label	1	G1: Exclusion diet (standard meds) G2: Unrefined carbohydrate, fibre-rich (standard meds)	G1: Low fibre advice (dose: NR) G2: High fibre advice (dose: NR)	12-m	*Clinical:* No difference between groups in disease activity at 12 months *Physiology:* No difference between groups in orosomucoid concentration or erythrocyte sedimentation rate at 12 months

Table 2.7 Randomised controlled trials of fibre interventions in adult patients with pouchitis

Reference	Patient details	Study details			Intervention details		Outcomes
	Disease ***N recruited*** ***N evaluated*** ***Male : Female***	***Design***	***Jadad***	***Groups***	***Details by group***	***Duration***	***Clinical and physiological outcomes:*** ***between and within groups***
Welters et al 2002[216]	Remission 20 recruited 19 evaluated 9 M : 10 F 37 yrs	Double blind Placebo RCT Cross-over	4	G1: Placebo, plus supplement drink G2: Prebiotic fibre, plus supplement drink	G1: Supplement (400 mls) G2: Supplement (400 mls) + 24 g/d inulin	3-w	*Clinical:* Significantly lower disease activity index (PDAI) in G2 (*p<0.01*) Significantly lower PDAI (endoscopic) in G2 (*p<0.04*) *Physiology:* Increased faecal butyrate concentration in G2 (62% increase compared to G1) No difference between groups in total lactobacilli and bifidobacteria Significantly lower *B. fragilis* in G2 (*p=0.02*) No difference between groups in total lactobacilli and bifidobacteria Significantly lower *B. fragilis* in G2 (*p=0.02*)

Table 2.8 Fibre and IBD: Summary of fibre effects on disease activity compared with control group

Study Ref:	Disease Stage	Study aim	Effect on disease activity between groups (score, remission, relapse rates)	Summary Effect on disease activity
Ulcerative Colitis				
194	Remission	Maintenance	Equivalent relapse rates to drug treatment	Positive
196	Remission	Maintenance	Reduced relapse rate *versus* no fibre	Positive
201	Active	Treatment	Reduced disease activity *versus* no intervention	Positive
199	Active	Treatment	No effect on disease activity *versus* placebo	No effect
200	Active	Treatment	No effect on disease activity *versus* placebo	No effect
202	Active	Treatment	No effect on disease activity *versus* no intervention	No effect
195	Remission	Physiological	Disease activity not reported	Not reported
197	Remission	Physiological	Disease activity not reported	Not reported
198	Active	Physiological	Disease activity not reported	Not reported
203	Mixed	Physiological	Disease activity not reported	Not reported
Crohn's disease				
207	Remission	Maintenance	Equivalent relapse rates *versus* low fibre	Equivalence
211	Active	Treatment	Equivalent remission rates *versus* low fibre	Equivalence
215	Mixed	Treatment	Equivalent disease activity *versus* exclusion diet	Equivalence
204	Remission	Maintenance	No effect on relapse rates *versus* placebo	No effect
205	Remission	Maintenance	No effect on relapse times *versus* placebo	No effect
208	Active	Treatment	No effect on remission rates *versus* placebo	No effect
209	Active	Treatment	No effect on remission rates *versus* placebo	No effect
213	Mixed	Treatment	No effect on disease activity *versus* placebo	No effect
214	Mixed	Maintenance	No effect on disease activity of low fibre *versus* normal diet	No effect
206	Remission	Maintenance	Reduced relapse times in high fibre *versus* low fibre	Negative
210	Active	Physiological	Disease activity not reported	Not reported
212	Active	Physiological	Disease activity not reported	Not reported
Pouchitis				
216	Remission	Treatment	Reduced disease activity *versus* placebo	Positive

2.6 Discussion: efficacy of fibre in IBD

In this systematic review of fibre in IBD, three studies in UC and the sole study in pouchitis reported a positive effect of fibre supplementation on disease activity outcomes (**Table 2.8**). These effects included equivalence of psyllium to mesalamine[194], additional benefit when the two are used concomitantly[194 196], extended maintenance of remission of UC[194], and reduced disease activity scores with the use of germinated barley fibre in active UC[201]. The sole study in pouchitis reported that inulin lowered disease activity scores during disease remission[216].

In CD, no studies showed fibre to have a significant impact on disease activity when comparing between groups, although one very small dietary intervention study did show improvement in quality of life in patients with active CD on a wheat-bran enriched high fibre diet[212]. Meanwhile, three studies showed equivalent effects of a high fibre diet compared with low[207 211] or fibre-excluded[215] diets in active[211], inactive[207] or mixed[215] CD. One further study reported that a low fibre diet had no impact on disease activity score compared with habitual diet[214] and another early study (conducted in 1985) reported a negative effect (greater relapse rates) of a high fibre compared with low fibre diet[206].

Despite the small number of studies (4/23) showing a between-group benefit for the efficacy of fibre supplementation on disease activity, a number of studies reported within-group benefits in the increased fibre group on alternative clinical or physiological outcomes. These included increased f. butyrate[194 216], reduced number or severity of gastrointestinal symptoms[195 196 199 210], reduced inflammatory markers[200 208], positive effects on inflammatory or immunological mediators[197 199 203 206 209], positive effects on microbiota[199 208 213] and improved histology[199 208 211 216] (**Tables 2.5, 2.6, 2.7**).

Whilst the positive effects were mostly evident in UC patients in studies employing supplement interventions it does not necessarily follow that increased fibre intake is not effective in CD or that dietary intervention is inappropriate. Of the three studies in

CD that returned equivalent results (**Table 2.9**) all used dietary interventions rather than supplements.

However, the systematic review of fibre in IBD showed that in general, UC was more amenable to therapeutic fibre interventions than CD. The superior efficacy of fibre in UC patients may be linked to the formation of its fermentation products, SCFA and in particular butyrate, in the colon at the site of the disease. Approximately 26% of patients with CD have inflammation regionalized only to the small intestine, with another 43% having both small and large intestinal inflammation[218]. Therefore, in the majority of patients with CD, inflammation occurs at least in part, proximal to the site of fibre fermentation. Two studies have reported increased faecal or colonic butyrate[194 216] in the high fibre group, one in UC[194] and one in pouchitis[216]. Restriction of dietary fibre in patients with IBD, on the basis of the results from this systematic review seems inappropriate[219].

2.7 Weight of evidence in support of conducting a second systematic review

The data emerging from the systematic review of fibre in IBD suggests that there is evidence for the potential efficacy of increased dietary fibre in IBD. In addition to those studies which returned positive between group effects of increased fibre intake on disease activity outcomes, a number of studies demonstrated positive within-group effects of increased fibre intake on inflammatory mediators or indicators of inflammation.

It is concluded that there is sufficient weight of evidence to conduct a second systematic review to evaluate whether any evidence exists regarding the efficacy of dietary fibre in preventing gastrointestinal inflammation, symptoms (or toxicity) in patients receiving pelvic radiotherapy and if data does exist, to assess whether it is sufficiently robust to accept or reject the hypothesis posed in this thesis.

As an aside to the thesis and with reference to patients with IBD, the evidence from the review of fibre and IBD suggests that in those patients without overt risk of bowel obstruction, restriction of dietary fibre is unnecessary but that all patients should be appropriately monitored regarding tolerance to fibre intake.

2.8 Methods for systematic review: efficacy of fibre during pelvic radiotherapy

2.8.1 Selection of sources and search terms

Seven electronic databases were selected for searching (**Table 2.9**).

Table 2.9 Electronic databases interrogated for systematic review: fibre & RT

Online database	Years searched	Limits applied		
Radiation-induced GI toxicity		***Adults***	***Study design***	***Humans***
MEDLINE	1956 - October 2013	*No*	*No*	*No*
EMBASE	1947 - December 2013	*No*	*No*	*No*
CINAHL (Nursing database)	1983 - 2013	*No*	*No*	*No*
Cochrane CENTRAL Library	All years available	*No*	*No*	*No*
CAB Direct (Nutrition)	All years available	*No*	*No*	*No*
Web of Science	1900 - December 2013	*No*	*No*	*No*
Scopus	1996 – December 2013	*No*	*No*	*No*

Terms and syntax differed for each database and varied from the previous systematic review due a less established literature on the topic of nutritional intervention during irradiation (**Table 2.10**).

Table 2.10 Search terms electronic database searching: fibre & RT

Medline and Embase
1. (((Dietary adj1 Fibre) or Dietary) adj1 Fib*).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] 2. Dietary Fibre/ 3. (Non-starch polysaccharide or NSP).mp [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

Table 2.10 Search terms electronic database searching: fibre & RT

4. Cellulose.mp. or Cellulose/
5. Methylcellolose.mp. or Methylcellulose/
6. Cereals/ or Cereal*.mp.
7. (Residue adj1 Diet).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
8. Roughage.mp.
9. (Bran or (Oat and Diet)).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
10. Psyllium.mp. or Psyllium/
11. Plantago/ or Plantago*.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
12. (Ispaghula* or ispaghulahusk).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
13. (Metamucil or Fybogel or Isogel or Reguval or Normocol).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
14. Sterculia.mp. or Sterculia/
15. Senna Extract/ or Senna*.mp.
16. Benefiber.mp
17. Pectin.mp. or pectins/
18. Guar gum.mp.
19.Prebiotics.mp. or prebiotics/
20. (Prebiotic* or Synbiotic).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
21. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22. (Diet* or Nutritional intervention or Formula* or Supplement*).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
23. 21 or 22
24. (Radiotherapy or Therapeutic Irradiation).mp [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
25. (Radiation and (Enteritis or Enteropathy or Toxicity or Injury or Side Effects or Proctitis or Mucositis)).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
26. 24 or 25
27. 23 and 26

CINAHL

http://search.ebscohost.com/login.aspx?direct=true&db=cin20&bquery=((((((%22Dietary+Fibre%22)+or+(MH+22Dietary+Fibre%22)))+OR+((%22Non+starch+polysaccharide+OR+NSP%22))+OR+(((%22cellulose%22)+OR+(MH+%22Cellulose%22)))+OR+(methylcellulose)+OR+(522roughage%22)+OR+((%22Bran+OR+Oat%22))+OR+(((%22Psyllium%22)+OR+(MH+%22Psyllium%22)))+OR+(Plantago*)+OR+(Ispaghula*)+OR+(Sterculia)+OR+(Senna*)+OR+(Benefiber)+OR+(Pectin)+OR+((%22Guar+Gum%22))+OR+(((%22Prebiotics%22)+OR+(MH%22Prebiotics%22)))+OR+((%22Prebiotic*+or+Synbiotic%22))+OR+(%22Metamucil%22)+OR+(Fybogel)))+OR+(((%22Diet*%22)+OR+((%22Nutritional+Intervention%22))+OR+(%22Formula%22)+OR+(%22Supplement%22)))))+AND+(((((%22Radiotherapy%22)))+OR+(MH+%22Radiotherapy%22)))+OR+((%22Therapeutic+irradiation%22)+OR+((%22Radiation+Enteritis%22))+OR+((%22Radiation+Enteropathy%22))+OR+((%22Radiation+Toxicity%22))+OR+((%22Radiation+injury%22))+OR+((%22Radiation+side+effects%22))+OR+((%22Radiation+proctitis%22))+OR+((%22Radiation+mucositis%22)))))&type=1&site=ehost-live

Table 2.10 Search terms electronic database searching: fibre & RT

CENTRAL (Cochrane Database)

#1(Radiation) and (Enteritis OR Enteropathy OR Toxicity OR Injury OR Side Effects OR Proctitis OR Mucositis)#2(Radiotherapy or Therapeutic Irradiation) #3(Dietary Fibre OR Dietary Fibre OR Non starch polysaccharide OR NSP OR cellulose OR methylcellulose OR cereal* OR "Residue Diet" OR Roughage OR Bran OR Oat AND Diet OR Psyllium OR Plantago* OR ispaghula* OR Metamucil OR Fybogel OR Isogel OR Reguval OR Normocol OR Sterculia OR Senna OR Benefiber OR Pectin OR Guar gum OR Prebiotic OR Synbiotic) #4(Diet* or Nutritional Interventional Formula* or supplement*) #5((#1 OR #2) AND (#3 OR#4))

CAB Direct

(Dietary Fibre OR Non Starch Polysaccharide OR NSP) OR (Cellulose OR Methylcellulose OR Cereal OR Residue Diet OR Roughage OR Bran OR Oat OR Psyllium OR Plantago OR Ispaghula OR Metamucil OR Fybogel OR Isogel OR Reguval OR Normocol OR Sterculia OR Senna OR Benefiber OR Pectin OR Guar gum OR Prebiotic OR Synbiotic) OR (Diet* OR Nutritional Intervention OR Formula* OR Supplement*) AND (Radiotherapy OR Therapeutic irradiation OR Radiation Enteritis)

Web of Science

#1:TS=("Dietary Fibre" OR 2Dietary Fibre" OR "Dietary Fib*"OR Non starch polysachharide OR NSP OR Cellulose OR Methylcelluloe OR Cereal* OR "Residue Diet" OR Roughage OR Bran OR Oat AND Diet OR Psyllium OR Plantago* OR Ispaghula OR Metamucil OR Fybogel OR Isogel OR Reguval OR Normocol OR Sterculia OR Senna OR Benefiber OR Pectin OR Guar gum OR Prebiotic OR Synbiotic) #2: TS=(Diet* OR Nutritional Intervention OR Formula* OR Supplement*) #3:#2 OR #1, #4: TS=(Radiation), #5: TS=(Enteritis OR Enteropathy OR Toxicity OR Injury OR side effects OR Proctitis OR Mucositis) #6: #4 AND #5, #7: TS=(Radiotherapy OR Therapeutic Irradiation) #8: #6 AND #7, #9: #8 AND #3

SCOPUS

((((("Dietary Fibre" OR "Dietary Fibre" OR "Dietary Fib*"OR non starch polysaccharide OR nsp OR cellulose OR methylcellulose OR cereal* OR "Residue Diet" OR roughage OR bran OR oat AND diet OR psyllium OR plantago* OR ispaghula* OR metamucil OR fybogel OR isogel OR reguval OR normocol OR sterculia OR senna OR benefiber OR pectin OR guar gum OR prebiotic OR synbiotic) AND ((diet* OR nutritional intervention OR formula* OR supplement)))) AND ((((radiotherapy OR therapeutic irradiation)) OR ((radiation)) AND (enteritis OR enteropathy OR toxicity OR injury OR side effect* OR proctitis OR mucositis)))))

Hand searching spanned the period 2001 – 2013 (**Table 2.11**).

Table 2.11 Hand searching sources: fibre & RT

Organisation / Event	Relevant publication(s)
ASTRO (American Society for Radiation Oncology)	Int. J. of Radiation Oncology Biology & Physics
UKRO (UK Society for Radiation Oncology)	Clinical Oncology, J Royal College of Radiologists
ESTRO (European Society for Radiation Oncology)	Radiotherapy and Oncology

2.8.2 Inclusion and exclusion criteria

Inclusion and exclusion criteria were defined according to the PICOS structure and are detailed in **Table 2.12**

Table 2.12 Inclusion and exclusion criteria: fibre & RT

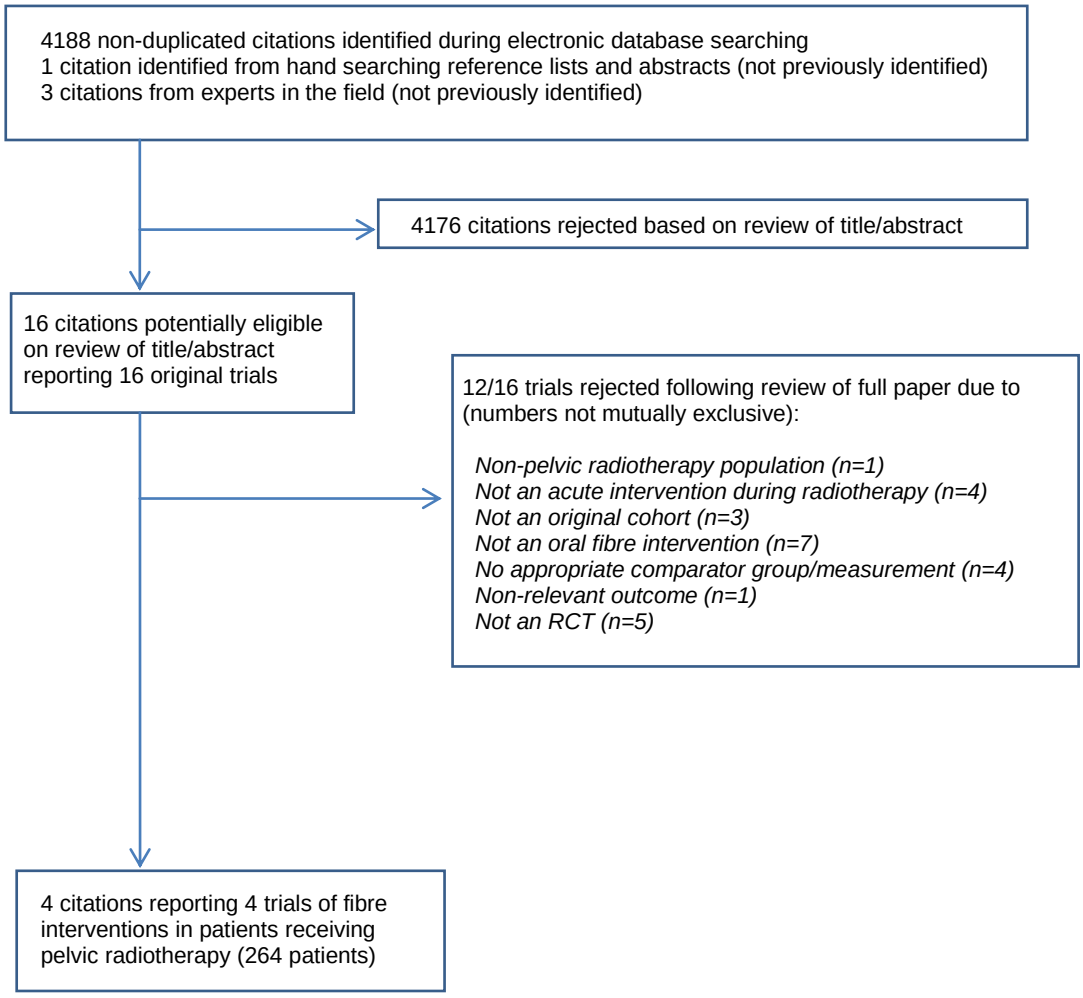
PICOS	Inclusion and exclusion criteria	Data extracted
Patient	Adult (in- or out-patients) over 18 y receiving radical radiotherapy for pelvic malignancies (acute setting only). Original cohorts only (i.e. excluding previous reports and abstracts of the same patients) to avoid duplication of patient numbers.	Location, clinical setting, age, gender, number of patients recruited, number of patients evaluated (i.e. those with evaluable data at study end). Cancer location, pelvic site, radiotherapy dose, duration of treatment, concomitant chemotherapy.
Intervention	Oral pharmacological fibre supplement, food supplement or dietary advice to increase or decrease fibre intake were eligible. Fibre interventions were required to meet the acknowledged definitions of fibre (15-17), and therefore included prebiotic fibres. Synbiotic preparations containing a named prebiotic fibre complying with the cited fibre definitions were also eligible irrespective of probiotic species and strain(s) used.	Fibre source, dose, presentation and period of administration. Presence of co-administered 'standard' medication(s) or supplemental nutritional substances. Compliance with interventional dose (if reported) and method of computing compliance. Genus/species/strain of probiotic if administered in conjunction with synbiotic preparation.
Comparators	Reports including a comparator group of either a placebo, no dietary intervention, an alternative dietary intervention or a pharmacological intervention were included. Reports comparing doses of fibre without any other comparator group were excluded.	Patient numbers in the intervention and comparator groups and nature of intervention. Group names standardised to avoid confusion.
Outcomes	Clinical outcomes or endpoints including: bowel habit and treatment-related toxicity, medication use, symptoms, quality of life, histology. Physiological outcomes or endpoints related to gastrointestinal inflammation including histology, inflammatory and immunological markers, microbiota and metabolic substrates. Presence or absence of adverse events related to interventional substrate.	Specific toxicity questionnaire scores or histology scores. Otherwise all other relevant clinical or physiological outcomes or endpoints at relevant time-points including statistical significance if reported. Comparisons of endpoint data between groups were extracted where possible, but within group comparisons between baseline and follow-up were extracted where of interest.
Study design	Randomised controlled trials (RCT). Open label, wholly or partially blinded or placebo-controlled nutritional interventional studies. Single or multi-centre. English or foreign language. Non-RCTs and uncontrolled trails excluded.	Type of study design, nature of blinding, active interventional period and duration of follow-up. Authors and publication details. Abstract or full report. Language of publication.

2.9 Results of the systematic review: efficacy of fibre during pelvic radiotherapy

2.9.1 Results of the search process

A total of 4192 non-duplicated papers were identified. Titles and abstracts of each were reviewed and 16 papers were potentially eligible. Following full review, only 4 papers (detailing 4 eligible studies) fulfilled the inclusion criteria and were included in the review (**Figure 2.2**).

Figure 2.2 Fibre and radiation-induced GI toxicity: summary of review process and results



All studies were reported in full (i.e. none as abstracts) and published in English language[130 220-223]. Study locations included United Kingdom, Canada, Sweden and Spain. Of the six experts contacted, all responded and three articles were identified that had not previously been identified through electronic searching (**Figure 2.2**)[130 220 223].

2.9.2 Patients, interventions and comparators

The four studies recruited 264 patients, comprising 19% of patients with mixed gynaecological cancers, 68% with prostate cancer and for the remaining 13% the pelvic site at recruitment was not reported. All patients were treated with 45 Gy or above to the pelvis in 1.8 – 2.0 Gy fractions with radiotherapy treatment periods of between 5 and 7 weeks.

The use or not of concomitant chemotherapy was not reported in one study[220] and not administered in one study as it included only prostate cancer patients[222]. In the remaining study[223], it is reported that patients who received previous or adjuvant chemotherapy were not eligible for inclusion in the study[223].

One study[220] was therapeutic in aim, designed to evaluate the efficacy of the fibre supplement Fybogel *versus* codeine phosphate for the treatment of new onset radiation-induced diarrhoea[220]. Two studies[130 222] were preventative in design, with the aim of examining dietary fibre manipulation in the prevention of radiation-induced GI toxicity. One used a fibre supplement in combination with a reduced insoluble dietary fibre intake[130] and the other a soluble fibre rich diet[222]. Both aimed to examine the effect of the intervention on incidence and severity of new-onset of diarrhoea.

For one of these studies, the first author was contacted to clarify that the nature of the study was therapeutic in aim as this was not clear from the published article [130]. The remaining study was physiological in aim and designed to examine the effect of a prebiotic supplement on microbiota dynamics although surrogate inflammatory markers were also measured[223]. All four studies employed a two-way group

comparison of which three used an open label design[130 220 222], one of which employed a cross-over design[220] and one a double blind placebo controlled design[223]. One study used a dietary intervention based on dietary advice and patient coaching[222] whilst three used soluble fibre supplements[130 220 223]. All employed multiple interventions, using additional single or multiple dietary restrictions in combination with fibre supplements (**Table 2.13**).

Table 2.13 Fibre and radiation-induced GI toxicity: summary of study interventions

Reference	Primary Intervention	Additional Dietary Restrictions		
		Low (insoluble) Fibre	***Low Lactose***	***Low Fat***
Lodge[220]	Soluble fibre supplement	√		
Murphy[130]	Soluble fibre supplement	√		√
Pettersson[222]	Soluble fibre rich diet	√	√	
Garcia-Peres[223]	Prebiotic supplement	√	√	

Intervention periods spanned active radiation treatment periods. In two studies, the intervention continued for 21[223] and 28[130] days after the last fraction of radiotherapy. One study is currently ongoing with patients being asked to continue the intervention up to 24m after cessation of radiotherapy[222]. Fibre doses were reported in 2/4 studies and varied from 12 g/d inulin/FOS[223] to '1 to 2 teaspoons', equivalent to 8 to 12 g/d, of a psyllium-based supplement[130].

The sole dietary intervention study was unable to report absolute insoluble or soluble fibre intake, or change in intake, as it employed a Food Frequency Questionnaire (FFQ) with no information on portion sizes[222]. Compliance was reported in two studies[130 222]. One of these studies asked patients to record dose consumed (teaspoons) in symptom dairies but did not report the results or quantify fibre intake from dietary sources[130]. The other used an FFQ based scoring system to reflect compliance although was unable to report quantitative information[222].

2.9.3 Study quality and adverse events

Quality scores (Jadad scale) reflected the fact that only one study employed a placebo controlled design. Three studies scored three points (of a maximum 5) and one study scored one point. No studies reported serious or adverse events resulting from the intervention. However, one was terminated early on safety grounds due the lack of efficacy of the fibre supplement intervention *versus* standard medication as a treatment for radiation-induced diarrhoea[220].

2.9.4 Clinical and physiological outcomes

2.9.4.1 Fibre for the prevention of radiation induced GI toxicity

Two studies examined the benefit of manipulating fibre intake for the prevention of radiation-induced GI toxicity during pelvic radiotherapy[130 222]. Each used a different intervention comprising a low fibre + low fat diet combined with soluble fibre supplement[130] and a high soluble fibre + low insoluble fibre diet combined with low lactose[222].

In the earlier of these studies, Murphy et al., recruited 84 patients and randomised them to receive either a daily dose of psyllium (Metamucil) in combination with standard dietary advice (i.e. low fibre + low fat diet) or dietary advice alone[130]. A bespoke diarrhoea scale termed the Murphy Diarrhea Scale was devised to calculate severity of on-treatment diarrhoea (**Table 2.14**). Patients were instructed to record the number of days during radiotherapy on which they experienced a 'diarrhoea day' defined as follows:

- 4 to 6 bowel movements > normal
- 1 or more watery bowel movements
- 2 to 3 loose or poorly formed bowel movements > normal
- Use of anti-diarrhoea medication

The number of diarrhoea days per patient was then summed to give a mean Murphy Diarrhea Scale severity score for each group (**Table 2.14**). However, 25% of patients

were excluded from the analysis, due to failure to return symptom diaries leaving 60 patients with evaluable data.

Table 2.14 Murphy Diarrhoea Scale severity rating and 'MDS' Score

Diarrhoea severity	MDS Score
Mild diarrhoea: <11% days with diarrhoea	**1**
Moderate diarrhoea: 11 - 20% days with diarrhoea	**2**
Severe diarrhoea: >20% days with diarrhoea	**3**

A significant difference (p=0.030) was reported in the mean diarrhoea severity score between groups in favour of the Metamucil group with mean Murphy Diarrhea Scale score of 1.8 ± 0.96 points *versus* the no intervention group with a mean severity score of 2.33 ± 0.84 points[130]. Incidence of diarrhoea was also reported to be significantly reduced (p=0.049) in the Metamucil group at 60% (18/30 patients) compared with 83% (25/30 patients) in the no intervention group[130]. Mean time to onset of diarrhoea, duration of diarrhoea and percentage of days on which anti-diarrhoeal medications were taken was not significantly different between groups.

Whilst this study showed a benefit for Metamucil supplementation the difference in the Murphy Diarrhea Scale severity score whilst significant was modest and included wide standard deviations compared to the mean difference obtained[130]. The authors acknowledged this was a pilot study and that accrual to the study was limited by resource constraints but argued that the number of patients recruited were sufficient for statistical analysis. However the study was not statistically powered for a specific endpoint. Further the MDS, although based on previously published scoring systems, is not a validated tool and it would have been useful if a more commonly used tool (CTCAE or RTOG) had been used for comparison purposes.

Nevertheless the Murphy Diarrhea Scale represents an interesting attempt to define a diarrhoea day in different ways of relevance to patients and importantly recognises that subsequent ranking of patient-reported outcomes into a composite 'severity'

score facilitates analysis. However individual patients' interpretation of watery or poorly formed bowel movements is subjective and whilst this could be improved with the use of visual materials or individual coaching these methods are rarely employed and labour-intensive to develop and test. Unfortunately this open label study failed to measure and/or report on dietary fibre or fat intake and did not comment on possible cross-talk between patients in different study groups both of which may have influenced results. Recruitment took place at two sites and advice given to patients was standardised with the use of a locally-produced hospital booklet[130].

In the second, eligible open label study, Pettersson et al, recruited 130 men receiving radiotherapy for localised prostate cancer (i.e. without lymph node involvement) and randomised them to receive standard care (i.e. to continue with their habitual diet) or a dietary intervention in which they were advised to avoid foods high in insoluble fibre and lactose in favour of foods high in soluble fibre and low in lactose[222]. A bespoke Food Frequency Questionnaire (FFQ) comprising 14 food groups with 6 groups low, and 8 groups high in insoluble fibre and lactose was designed to guide patients' food choices and monitor adherence to dietary instructions. The FFQ was used in both standard care and intervention groups. Patients were interviewed immediately before the start of radiotherapy and at 4 weeks and 8 weeks from the start of treatment, and two months following radiotherapy treatment.

Radiotherapy-induced toxicity was assessed using the prostate-specific QLQ-PR25 and EORTC QLQ-C30 together with a non-validated study-specific Gastrointestinal Side Effects Questionnaire (GISEQ) which assessed 'bother' associated with diarrhoea, blood in stool, mucous discharge, intestinal cramps, intestinal pain, intestinal gas and flatulence[222]. At two-months from treatment commencement there was an attrition rate of 12% (58/66 patients) in the standard care group and 14% (55/64 patients) in the intervention group. Analysis of compliance reported an interaction effect (p<0.001) between randomisation and time in the FFQ scores at the 8 week follow-up point indicating that both groups adhered to dietary instructions[222].

However, despite a trend towards reduced incidence of symptoms (using selected variables taken from the QLQ-PR25) no significant differences between groups in any gastrointestinal toxicity or quality of life measures were found. Incidence of self-reported diarrhoea at 8 weeks or end of radiotherapy was slightly less in the interventional group 30% (14/51 patients) *versus* the standard care arm 33% (19/60 patients) but not significant[222].

There are a number of reasons why this study may have failed to detect a significant difference between groups. The authors acknowledge that the study may have been underpowered. Much lower rates of on-treatment toxicity were observed than expected. Thirty percent of patients reported presence of bowel symptoms at randomisation whilst just 50% reported presence of gastrointestinal symptoms during treatment. Thus larger numbers would have been required to detect such small differences in toxicity. The low toxicity rates experienced may have reflected the size of the radiotherapy treatment field. Conformal prostate radiotherapy includes a small portion of the rectal wall immediately adjacent to the prostate gland but generally does not include other portions of the large or small intestine, both of which cannot be avoided when irradiating the prostate gland and pelvic nodes.

Thus, if the study had included patients with nodal involvement, higher rates of toxicity may have been observed. It is also possible that the dietary adjustments made by patients were ineffective. However, quantitative values for differences between groups in fibre or lactose intake could not be extrapolated from the FFQ which contained no details on portion size. Many of these points are acknowledged by the authors[222]. Study outcomes are summarised in **Table 2.15**.

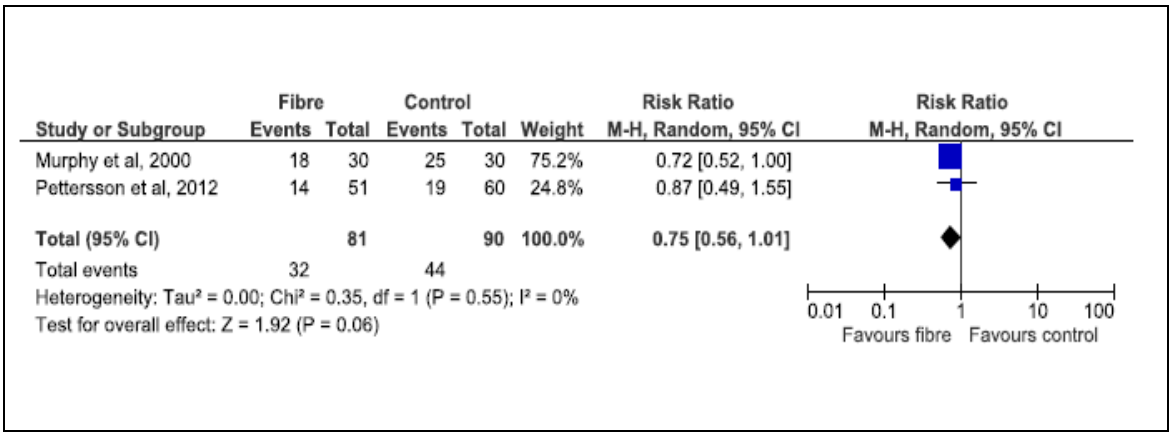
In contrast to the IBS systematic review, for the radiation-induced GI toxicity systematic review, meta-analysis was considered appropriate to assess whether the dietary fibre intervention had an effect on the endpoint, incidence of new-onset diarrhoea during radiotherapy, as reported in the above two studies[130 222]. A random effects model was chosen due to the differing experimental design of the two studies and in consultation with Ms Eirini Dimidi, King's College London who advised and

assisted with this analysis. The risk ratio (RR)[190] or relative risk was used to compare the efficacy of a dietary fibre intervention (experimental group) versus no intervention (control group) where:

$$RR = \frac{\text{Risk of the event in the experimental group}}{\text{Risk of the event in the control group}}$$

In the analysis depicted below in the form of a forest plot, the Risk Ratio (CI) of 0.75 (0.56, 1.01) indicates that the probability of new onset diarrhoea in the treatment groups is 25% less than that in the control (or standard care) groups, therefore favouring a fibre intervention. However, the test for the overall effect is not statistically significant, falling just short of the accepted level of statistical significance (*p*=0.06).

Figure 2.3 Forest plot comparing fibre interventions and incidence of diarrhoea



2.9.4.2 Fibre for the treatment of radiation-induced GI toxicity

One study in female patients receiving radiotherapy for gynaecological cancer (**Table 2.15**) examined the efficacy of a soluble fibre supplement, ispaghula husk (Fybogel) for the control of radiation induced diarrhoea[220]. Using an open label cross-over design patients were randomly assigned to receive Fybogel or standard medication, codeine phosphate, at new onset of treatment-related diarrhoea, defined as 'excessively frequent and loose bowel movements'. In addition, all patients were advised to follow a low residue diet (not defined) whilst on radiotherapy treatment. The trial was closed

after ten patients had been randomised to the study (five per arm) due to a reported lack of bowel control in the Fybogel group. All patients in this group were crossed-over to standard medication.

Although 2/5 patients in the Fybogel group reported improvements in stool consistency they found the supplement unpalatable and difficult to swallow and did not wish to continue taking it. In contrast all patients randomised to receive codeine phosphate regained what was termed normal bowel control. The authors reported that ispaghula husk was not totally ineffective at controlling diarrhoea but nevertheless concluded that it was a less effective and less palatable preparation than codeine phosphate[220].

2.9.4.3 Physiological effects of fibre during pelvic radiation

One study has explored the efficacy of a fibre-based prebiotic supplement for the promotion of beneficial bacterial species, *Lactobacillus* and *Bifidobacterium* during pelvic radiotherapy[223]. In a randomised, double-blind placebo controlled design, 40 patients with gynaecological cancer receiving post-operative radiotherapy (of whom 31 provided evaluable data) were randomised to receive either 6g of an inulin / fructo-oligosaccharide (FOS) mixture in a 50:50 ratio twice daily or placebo (**Table 2.15**). The intervention commenced one week prior to start of radiotherapy and continued for three weeks after the last fraction of treatment. All patients were additionally advised to avoid foods high in insoluble fibre and lactose.

Faecal samples were obtained at four time-points and analysed using cell culture and fluorescent in-situ hybridisation (FISH) methods. Inflammatory marker faecal calprotectin and faecal DNA as a marker of epithelial desquamation were also analysed. Results indicated that during radiotherapy, counts of both *Lactobacillus* and *Bifidobacterium* were significantly reduced in both groups. However three weeks after treatment there was a significant increase in the number of both *Lactobacillus* and *Bifidobacteria* in the prebiotic group (p=0.04 and p=0.03 respectively) compared to placebo which led the authors to conclude that the inulin/FOS mix improved recovery of both genera after radiotherapy.

No significant difference between groups was found in inflammatory marker faecal calprotectin or faecal DNA and unfortunately the published article did not include any data in respect of either of these inflammatory or mucosal damage-related markers. Further, although no adverse effects were reported resulting from the intervention, the study failed to assess clinical endpoints[223]. No information was provided regarding the recommended on-treatment diet nor of patients' compliance with this during radiotherapy. The authors state that a study using a similar intervention in a similar patient group is currently underway and that this study will include clinical variables and a quality of life questionnaire[223].

Table 2.15 Randomised controlled trials of fibre interventions in adult patients receiving pelvic radiotherapy

Reference	Patient details	Study details	Radiotherapy treatment details		Intervention		Outcomes (Acute)
	N recruited *N evaluated* *Male : Female* *Age*	*Study Design* *[Jadad score]* *Intention*	*Dose (Gy)* *Fraction (#)* *+/- CT*	*Pelvic sites* *(Number of patients)*	*Details by group (G1,G2,G3)* *Dose*	*Duration*	*Clinical outcomes:* *Compliance / tolerance (where reported)*
Lodge 1995[220] UK	10 recruited 10 evaluated 0 M : 10 F Age : NR	Open label Cross over [1] Therapeutic	45 Gy 1.8 Gy # CT : NR	Gynaecological cohort: Site(s): NR	G1: Standard medication (Codeine phosphate) plus low residue diet (not defined) G2: Ispaghulahusk plus low residue diet (not defined)	Intervention started on presentation of treatment induced diarrhoea	*Clinical:* Cessation of study after 5/5 patients in G1 responded to medication versus 0/5 in G2 who responded (*p<0.004*) Improvement in stool consistency and control following cross-over of G2 patients to G1 Patients in G2 reported intolerance to intervention including unpalatability (3/5 patients) and difficulty swallowing (1/5 patients)
Murphy 2000[130] Canada	84 recruited 60 evaluated 51 M : 9 F 65 yrs (M) 60 yrs (F)	Open label [3] Preventive	68 Gy 2 Gy # CT: NR	Mixed pelvic cohort: Prostate: 51 Gynaecological: 9	G1: Low fibre (dose NR), limited fat (dose NR) alcohol and caffeine G2: Low fibre (dose NR), limited fat (dose NR) alcohol and caffeine plus psyllium supplement (dose 1/2 teaspoons / day	Active treatment 4 - 5 weeks with 28d post-RT follow-up	*Clinical:* Significantly reduced incidence of diarrhoea (bespoke scale) in G2 versus G1 (*p=0.049*) Significantly reduced group mean severity of diarrhoea score (bespoke scale) in G2 versus G1 (*p=0.030*) No significant difference between groups in need for anti-diarrhoeal medication (*p=0.062*) Large number of patients (30%) not included in the final analysis due to inaccurate or incomplete data including failure to return bowel habit diaries.
Pettersson 2012[222] Sweden	130 recruited 112 evaluated 130 M : 0 F 66 yrs	Open label [3] Preventive	70 Gy 2 Gy # CT : None	Urological cohort: Prostate: 112	G1: Standard care: normal diet G2: Reduced lactose and insoluble fibre	Active treatment 7 weeks	*Clinical:* No difference between groups in total in total symptom scores nor in selected gastrointestinal symptoms No significant difference between groups in' patient-reported bother' from gastrointestinal side effects No difference in health-related quality of life scores between groups No correlation between bowel symptoms and level of adherence to dietary restrictions in G2
Garcia-Peres	40 recruited	Double blind	52.2 Gy	Gynaecological cohort:	G1: Placebo: 12g maltodextrin plus	Active	*Clinical:*

2012[223] Spain	31 evaluated 0 M : 31 F 58 yrs	[3] Physiological	1.8Gy # CT : None	Endometrium: 25 Cervix: 2 Uterus: 3 Vulva/vagina: 1	restricted fibre, lactose and fermentable dietary substrates including probiotics G2: Prebiotic: 12g (50% inulin, 50% FOS plus restricted fibre, lactose & fermentable dietary substrates (e.g. probiotics)	Treatment Including one week pre-RT And 3 weeks post-RT	Significant decrease in Lactobacillus and Bifidobacterium in both groups at end of radiotherapy compared to pre-radiotherapy levels Significantly increased Lactobacillus (*p=0.04*) and Bifidobacterium (*p=0.03*) in G2 three weeks after radiotherapy versus G1 No significant difference between groups during radiotherapy in levels of faecal calprotectin or excretion of human DNA

2.10 Discussion: efficacy of fibre during pelvic radiotherapy

In the systematic review of fibre in patients undergoing pelvic radiation the data in support of fibre intervention is equivocal. Only four RCTs exploring the manipulation of dietary fibre in this treatment setting were identified. One study reported a benefit for psyllium supplementation, in combination with reduced dietary fibre and fat intake, for the prevention of new-onset treatment-induced diarrhoea[130]. However, methodological criticisms of this study can be made regarding the lack of statistical powering and the use of non-validated outcome tools.

A further initially adequately powered study failed to demonstrate the efficacy of an insoluble fibre rich + low lactose diet for the prevention of new onset gastrointestinal symptoms, including diarrhoea, due to unexpectedly low rates of toxicity in the study cohort[222]. The two studies combined in meta-analysis showed a 25% reduction in the relative risk of developing new-onset treatment induced diarrhoea in the interventional groups but lacked significance (p=0.06). However, these studies were heterogeneous in nature employing different measurement tools, using differing interventions and recruiting cancer patients with differing pelvic malignancies.

One small therapeutic study found no benefit of psyllium versus standard medication for the control (i.e. treatment) of new-onset diarrhoea and was terminated early[220]. A final study using an inulin/FOS prebiotic intervention reported positive effects on beneficial microbiota species recovery following radiotherapy but did not measure clinical endpoints[223].

Unfortunately, in contrast to studies in IBD, 3/4 of the studies included in the systematic review of fibre during pelvic radiotherapy did not employ physiological endpoints to provide added insight as to fibre's possible mechanism of action[130 220 222]. The only study which investigated physiological mechanisms, the effect of a prebiotic on selected microbiota genera / species, failed to include clinical endpoints[223].

Methodological difficulties were apparent in the majority of studies. Use of multiple interventions, lack of robust data on fibre intake or compliance, use of non-validated

endpoints and recruitment of patients with heterogeneous treatment fields may have served to confound the true efficacy of fibre in this setting.

2.11 Weight of evidence in support of conducting a randomised controlled trial

Dietary fibre has physiological properties that may impact on gastrointestinal inflammation and therefore may be beneficial in the management of radiation-induced inflammation and toxicity. However, the data available from the four studies included in the systematic review of the efficacy of fibre in patients receiving pelvic radiotherapy is not sufficiently robust to answer the research hypothesis posed in this thesis.

The next step is to design an adequately powered, randomised controlled trial to assess the efficacy of manipulating dietary fibre intake in patients receiving pelvic radiotherapy.

2.12 Learning from the systematic reviews

The reviews have raised some interesting and important issues with respect to the choice of intervention for a new randomised controlled trial. The majority of studies identified in the two reviews used fibre supplements rather than dietary interventions and it is clear, that if a dietary-based interventional design is to be used for the randomised controlled trial it will be more time-consuming to administer than a supplement intervention and that double-blinding is virtually impossible.

Further, it is recognised that dietary interventions require the provision of definitive and meaningful guidelines to patients to ensure achievement of desired aims combined with rigorous monitoring and meticulous analysis if they are to provide meaningful data. This implies the use of validated tools for assessing dietary intake at appropriate time-points. Despite these drawbacks, dietary interventions are of course more physiological, and in contrast to fibre supplements, will comprise foods with differing but naturally occurring quantities of both soluble and insoluble fractions with mixed fermentative properties. Gut microbiota have evolved in response to host diet

and may respond differently to supplement as opposed to dietary intervention. Further, dietary interventions can be designed to be empowering rather than prescriptive and if appropriately designed, should be readily adaptable for the treatment (non-research) setting.

Another important message emerging from the two systematic reviews is that compliance with dietary intervention is a complex process and is not well defined or measured. In the first instance, compliance with a dietary intervention requires patients to understand the information being delivered to them (influenced by the skills of the health professional or researcher), to value it (influenced by their health psychology) and then have the ability to adopt it (influenced by their food access, food knowledge).

Unfortunately compliance was not robustly measured in many of the dietary intervention trials included in the two reviews undertaken in this thesis. Therefore, the extent to which the variable success of the dietary intervention studies was due to poorer study design, failure to achieve the dietary fibre target or a true lack of impact of fibre from dietary sources to manage gastrointestinal inflammation, is unclear. An intervention of advice to manipulate dietary fibre intake (increasing or decreasing intake) must therefore include some measure of compliance and if necessary take account of any confounding factors. Equally, and in a similar manner to the well-known placebo effect in clinical research, dietary intervention, simply through contact with the relevant health professional may positively affect outcomes. Minimising the potential role of bias with respect to the intervention is thus seen as another important aspect of any nutritional interventional randomised controlled trial.

Finally, although some studies in IBD did employ clinical and physiological endpoints, none in the radiotherapy setting adopted this approach. This is felt to be vital requirement since in the event of significantly differing outcomes associated with intervention, physiological endpoints may provide valuable insight as to the biological mechanism underlying any effect. Since dietary fibre is the nutritional intervention of choice, the inclusion of measurement of faecal short chain fatty acids would be a valuable adjunct to any new research conducted in this setting.

CHAPTER 3: Methods

Randomised Controlled Trial

3.1 Introduction to methods

There is a lack of robust evidence to support or refute the efficacy of increased dietary fibre in the management of gastrointestinal symptoms arising during pelvic radiotherapy. This chapter describes the methods used in the design and conduct of an adequately powered randomised controlled trial to investigate the role of fibre during pelvic radiotherapy.

The trial and all nutritional intervention material was designed by the author and drew on knowledge gained from the conducting of the two systematic reviews previously described. The trial was entitled ***'a randomised controlled trial to investigate the role of low or high fibre diets in patients undergoing pelvic radiotherapy',*** abbreviated to 'The Fibre Study'***.***

The trial rationale and design are described first, followed by a description of trial procedures. Methods used for collection of trial measurements follows and finally, statistical methods.

3.2 Clinical trial: design

3.2.1 Rationale

An estimated half of all newly diagnosed cancer patients will receive radiotherapy at some point in the course of their disease[4]. As the number of long-term post-radiotherapy cancer survivors continues to grow, preventing or reducing the side effects of irradiation treatment is becoming an increasing priority[224].

During radical pelvic radiotherapy treatment, more than 90% of patients develop gastrointestinal symptoms with 40% of patients requiring anti-diarrhoeal medication. At the author's institution, healthcare professionals frequently advise patients to reduce dietary fibre during pelvic radiotherapy to control these symptoms despite the lack of robust evidence in this respect.

As the systematic review of the efficacy of fibre in IBD has shown, there is evidence that fibre has a potentially beneficial effect on disease outcomes and may reduce

inflammatory processes[219]. Further, as the systematic review of fibre in patients receiving pelvic radiotherapy has shown, no adequately powered, single intervention, high quality, randomised controlled trials have examined the potentially beneficial effects of dietary fibre on gastrointestinal symptoms and inflammatory processes during pelvic radiotherapy.

The design of the fibre study was conceived by the author with input from associated professionals including the Trust's statistician, a consultant dietitian, research radiographer, gastroenterologist and nutritional / fibre expert. The study design was influenced by lessons learned from the two systematic reviews and as a result, particular emphasis was placed on the following requirements:

- The need for a robust, achievable, meaningful and measurable dietary intervention, including the provision of appropriate guidance to patients which they could readily assimilate and adopt with minimal additional burden.

- The need for the accurate capture and analysis of dietary intake, including fibre intake data using as far as possible gold standard methods of data capture and analysis via appropriate dietary software (i.e. analysis) tools.

- The need for an appropriate measure of compliance to ascertain whether patients were able to adopt and comply with the advice given and thus allow study investigators to ascertain whether an appropriate differential in fibre intake was maintained between study groups.

- The need for the inclusion of an appropriate physiological endpoint (SCFA) to provide insight regarding the mechanism of efficacy (or not) of the dietary fibre intervention.

- The need to employ objective measures of stool-related toxicity to allow for the analysis of the effects of radiotherapy and fibre intake on stool parameters in the absence of a clear and agreed definition of treatment-induced diarrhoea.

3.2.2 Aims and hypothesis

The primary aim of the study was to examine the effect of a low or high fibre diet, compared with a normal diet (i.e. a patient's habitual fibre intake) on gastrointestinal symptoms in adult patients receiving radical radiotherapy for pelvic malignancies. In view of the important relationship between the severity of toxicity experienced in the acute setting (i.e. during radiotherapy) and the risk of late effects, a single measure of gastrointestinal symptom burden was included one year after radiotherapy[31 32 34-36 38-40 46]. The data from this longer-term outcome of the study are currently maturing and will be reported separately.

The secondary aims were to assess the effect of low or high fibre diets on:

- Quality of life during and one year after radiotherapy
- Faecal SCFA concentration at start and end of radiotherapy
- Stool characteristics at start and end of radiotherapy
- Compliance with dietary intervention
- Nutritional parameters at start and end of radiotherapy, including weight, height, BMI, macro- and micronutrient intake

The research hypothesis (H_1) for the study was:

'A high fibre diet (defined as 18 - 22 g/d of non-starch polysaccharide) will reduce or prevent gastrointestinal symptoms in patients receiving radical pelvic radiotherapy. This benefit will be achieved at least partly by the anti-inflammatory action of short chain fatty acids (SCFA) resulting from the fermentation of soluble fibre by microbiota and partly through the beneficial effect of fibre on stool frequency and form '

3.2.3 Design: summary

The Fibre study was designed as a 3-arm, open label, nutritional intervention, randomised controlled trial. The author as principal study investigator was not blinded to the intervention. Further, it was not possible to blind patients to the intervention as

they would inevitably know whether they were receiving high fibre or low fibre dietary advice.

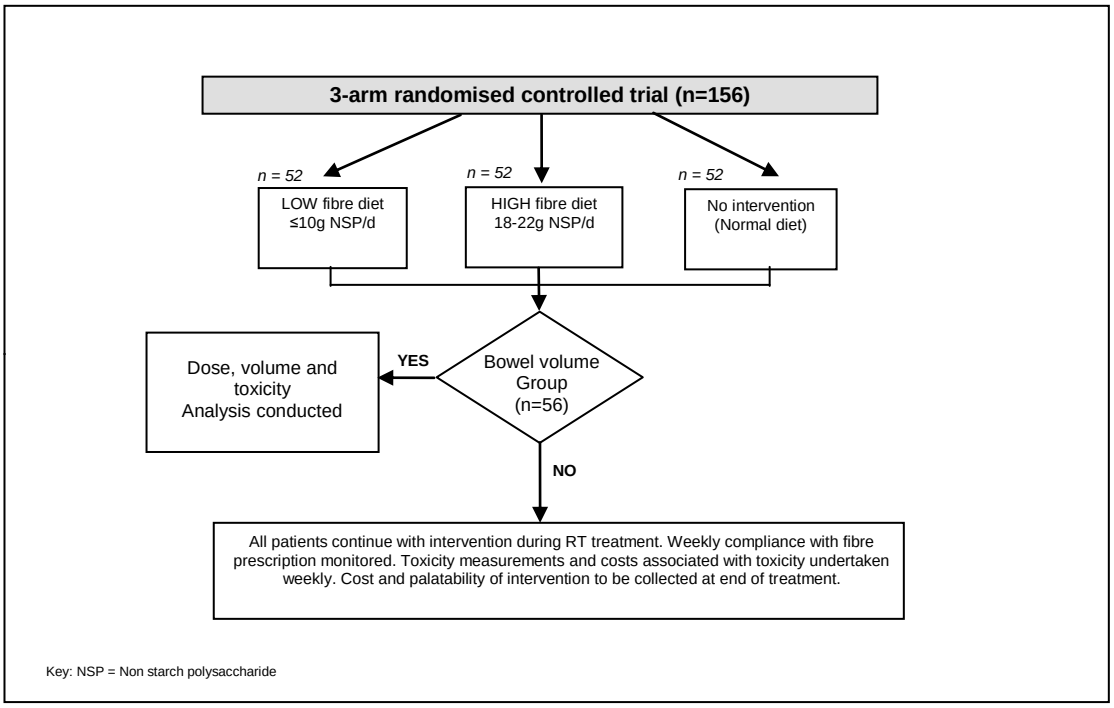
The time-table for the collection of study measurements was designed to ensure similar amounts of time in terms of contact minutes with the author (a registered dietitian) were given to all patients to standardise any effect of dietetic input alone as distinct from the effect of the intervention.

Patients randomised to the low fibre group and the high fibre group were given a target for daily dietary fibre intake and asked to follow a low or high fibre diet for the duration of radiotherapy. The control group were patients following their normal (habitual) dietary fibre intake. The low and high fibre groups received additional advice on how to achieve their required target fibre intake and also completed records detailing daily fibre intake to chart their compliance. All patients received standard medical care.

The initial trial design allowed for an exploration of the relationship between proportion of irradiated bowel and GI toxicity in a sub-group of 56 patients. The data from this aspect of the study are currently undergoing analysis and will not be reported within this thesis.

The study design is depicted in **Figure 3.1**.

Figure 3.1 Design of the randomised controlled trial



3.2.4 Patients

Patients eligible for the trial were adults due to receive a course of radical (long-course) radiotherapy for the control of pelvic malignancies. This included patients with a diagnosis of gynaecological cancer (endometrial, cervical, vaginal, vulvar, ovarian); urological cancer (locally advanced prostate and bladder) and cancers of the lower gastrointestinal tract (colon, rectum, anus) and given the proximity of healthy small and large bowel tissues to these target organs, all patients were at risk of GI toxicity.

Urology patients (locally advanced prostate and bladder cancers) were subsequently excluded from the study prior to recruitment commencing. This decision was made in view of the number of studies competing for this patient group and the emergence of new urology treatment protocols which would have resulted in increased heterogeneity in terms of volume of small and large bowel within the treatment field in the recruited sample.

Patients were excluded from the trial if:

1. They were unable or unwilling to give informed consent.
2. They were recruited to other studies where toxicity was a primary endpoint.
3. They had a condition precluding oral nutritional intake.
4. They had established wheat intolerance or have coeliac disease.
5. They had been prescribed low residue diet for a clear medical reason.
6. They had a gastrointestinal stent.
7. They had a jejunostomy, ileostomy or colostomy.

3.2.5 Radiotherapy treatment protocols

Radiotherapy treatments were delivered in compliance with local Trust protocols and employed External Beam (EBRT) and Intensity Modulated (IMRT) techniques. All patients received at least 45 gray (Gy) to the pelvis in 1.8 Gy fractions in daily exposures (Monday to Friday) of 10 to 20 minutes total (appointment) duration over periods of 5 to 7 weeks. Concomitant chemotherapy agents were used for selected tumour sites with the aim of sensitising tumour cells to irradiation.

Patients with gynaecological malignancies (cervix and endometrial cancers) received high or low dose brachytherapy treatment as an adjunct to external beam irradiation where indicated. Doses delivered using these (localised) techniques were not considered to contribute to GI toxicity and thus (in this trial) did not contribute to the computation of final radiotherapy dose.

Treatment planning comprised one computed tomography (CT) radiotherapy planning scan simulating treatment delivery. Tumour extent and organs at risk were outlined by clinicians on each CT slice. Dosimetry calculations, performed by medical physicists, defined the dose to be received by the tumour and adjacent healthy organs. Treatment margins of 1-2 mm were added to the clinical target volume to allow for inter- and intra-fraction organ motion and random and systematic variation in patient set-up.

Radiotherapy treatment protocols used at the author's institution are outlined in **Table 3.1**

Table 3.1 Radiotherapy treatment details for eligible patients

Pelvic site	Total EBRT Dose (Gy)	Fractionation [No. attendances]	Concomitant chemotherapy	Treatment duration (weeks)
Colon / rectum (phase 1)	45	1.8 [25]	Oral daily Capecitabine	5
Colon / rectum (phase 2: pre-op.)	3.4 - 9	1.8 [3 – 5]	as above	1
Colon / rectum (phase 2: post-op.)	9 - 14.4	1.8 [5 – 9]	as above	1 - 2
Anus (Phase 1: IMRT)	30.6	1.8 [17]	IV Mitomycin C plus oral daily Capecitabine	3 - 4
Anus (Phase 2: EBRT)	19.8	1.8 [11]	as above	2
Endometrium *	45	1.8 [25]	none	5
Cervix *	50.4	1.8 [28]	IV Cisplatin (4 cycles)	5 - 6
Vulva, vagina, Fallopian tube, ovary	45 - 55.8	1.8 [25 – 31]	Individual review	5 - 6

Key: * Plus brachytherapy using HDR delivery, typically 8Gy in 2 insertions (see section 1.3.1 for explanation)

3.2.6 Intervention

Examples of all interventional tools described in this section are given in **Appendix 1**. A dietary-based intervention, in preference to supplement, was selected for physiological and palatability reasons. In a previous prospective cohort study in prostate cancer patients, dietary-based adjustments of daily fibre intake had proven feasible and popular with patients in this setting[75].

In view of the differing therapeutic effects of soluble (highly fermentable) versus insoluble (poorly fermentable) fibre[225], the fibre study was originally designed as a 4-arm trial with the high fibre group split into soluble- and insoluble-rich groups. However, detailed consideration ruled this non-feasible. Firstly, it was felt that randomisation to the high fibre soluble-rich group would result in an unduly restrictive dietary regimen, unlikely to result in compliance. Secondly, there is poor discrimination in dietary software packages regarding estimation of poorly fermentable versus readily fermentable dietary fibre in food. This would have considerably complicated analysis.

There is no recommended daily fibre intake for adults in receipt of pelvic radiotherapy and as reported earlier in this thesis, the evidence from RCT of high fibre or fibre-restricted diets during pelvic radiotherapy is weak and inconclusive. Therefore, both high and low target fibre intakes, based on intakes for healthy adults in the UK, were selected for intervention[139]. Fibre targets were defined in grams per day of non-starch polysaccharide (NSP) calculated using the Englyst method of analysis[226].

A mean difference of 8g / day between the high and low fibre groups was postulated to demonstrate an effect of differing fibre intake if one existed. Thus the high fibre group were advised to consume between 18 and 22g of NSP per day (18g / day being the DRV for fibre intake for healthy adults in the UK[139]) and the low fibre group, no more than 10g per day. Both fibre targets (high fibre 18-22 g/d, low fibre ≤10 g/d) were deemed achievable for two reasons. First, with reference to fibre intake in healthy adults, mean average consumption of NSP for healthy adults (19 – 64 years) in London and the South East is 15.6 g/d per day (sd 6.06) for men and 13.0 g/d (sd 5.17) for women[227]. Second, with reference to a recent sample of men and women being treated with pelvic radiotherapy (n=44), mean daily fibre intake was assessed as being 14.0 g/day (sd 5.1) at the start of radiotherapy and 12.7 g/d (sd 4.8) following 4-5 weeks of treatment[228].

A guidance booklet entitled ‘Fibre in Foods’ was developed specifically for the trial by the author. This booklet listed the fibre (NSP) content of typical portions of commonly consumed food items. The design and ease of use of this booklet was considered to be

a key feature in assisting and motivating patients to comply with the intervention. The 16-page booklet, available in A4 or A5 sized versions according to patients' preference, contained 405 food items arranged into 10 major food groups.

Fibre (NSP) content of typical portions of all foods was detailed in the booklet as 'points' equating to grams of fibre per portion. Patients were encouraged to count their daily fibre intake using this booklet, in points or grams per day and to record this in an accompanying exchange diary. Advice on reading food labels and converting between imperial and metric units was included on the inside back cover of the booklet.

The fibre intake exchange diary, which accompanied the guidance booklet was intended to aid patient compliance with the high or low fibre interventions and did not constitute an outcome measure of fibre intake as the method is not validated for estimation of fibre intake. However, similar interventional strategies have been used successfully by our group and others in previous nutritional interventional research in oncology patients[76 229-231]. The guidance booklet and exchange diary were not made available to patients randomised to the control or normal diet group.

The exchange diary, which was of similar design for both the high and low fibre groups, comprised a series of tick boxes printed for each day of treatment. The high fibre version of the diary displayed a series of 22 clear boxes printed per line arranged in a week per page style, with availability for recording fibre intake for up to 6 weeks of radiotherapy treatment, including weekend (non-treatment) days. The low fibre version of the diary was similar except that boxes 11 to 22 were shaded rather than clear. Patients in the high fibre group were advised to consume at least 18 grams or points of fibre a day but not to exceed 22 grams. Patients in the low fibre group were advised to consume 10 grams or less per day and thus not to use the shaded boxes.

In addition to assisting patients with estimating their fibre intake, the exchange diary provided a useful starting point for discussion with them during treatment and allowed an immediate and approximate calculation of fibre intake by the principal trial

investigator (the author) in the clinical setting. Prior to use in the trial, the guidance booklet and accompanying exchange diary were trialled in 10 healthy volunteers.

The volunteers comprised dietetic and non-dietetic colleagues of the author, and friends and neighbours (males: 5, females: 4; age range 26 – 78 years). Suggestions made by volunteers to improve the layout and / or contents of the booklet were reviewed by the author and included as appropriate. The calculation of fibre intake, as a primary nutritional outcome measure, was accomplished using 7-day food diaries which were completed by patients in all trial groups during the first and last week of radiotherapy.

3.2.7 Selection of primary endpoint and trial powering

Treatment-induced toxicity is an ill-defined concept although bowel-related toxicity ranks as the most troublesome of all symptoms[232]. Minimising damage to healthy gastrointestinal tissue is of critical importance to ensure treatment completion without disruption and thus maximised possibility of tumour control. As discussed previously, non-invasive measurement of symptoms continues to be used for assessing toxicity. However validated indices for use in this setting such as the Radiation Therapy Oncology Group (RTOG) scoring tool[67] are surprisingly blunt. The Inflammatory Bowel Disease Questionnaire (IBDQ) is patient-completed and comprises 32 questions each with 7 grades of severity[233]. It takes a few minutes to complete and has been shown to be more sensitive in the acute and late radiotherapy setting than the RTOG[6 73].

The increased discriminatory power of the IBDQ coupled with its use in previous trials in the radiotherapy setting were key factors in selecting this tool for measuring GI toxicity in this trial[46 74-76]. Patients complete the entire 32 question IBDQ and are unaware of the IBDQ-B 'bowel domain' questions: 1, 5, 9, 13, 17, 20, 22, 24, 26 and 29. The modified McMaster IBDQ was used for the trial as the terminology in this version has been modified for use in the UK[72]. The difference between groups in the change in IBDQ-B score between baseline (day 1 of radiotherapy) and nadir (worst) score during treatment was selected as the primary endpoint for the trial.

A difference of 6 points between groups (representing a 10% difference in maximum possible change in IBDQ-B score) was selected as constituting a meaningful clinical difference. This compares with 'meaningful clinical improvement' in Crohn's patients of 1 point in two thirds of IBDQ questions[234] and '*significant improvement'* in ulcerative colitis patients or a rise in score of 20 points[235], both of which are equivalent to a 9% change in score. In four previous mixed pelvic cancer cohorts (n=390) comprising 52% of patients with urological, 18% gastrointestinal and with 30% gynaecological tumours, the mean change in IBDQ-B score between start and end of radiotherapy was 9.3 points (standard deviation: 8) representing a 15% change in score[24 46 75 76].

In order for the trial to have to 90% power (beta or probability of type 2 error of 10%) to detect a difference of 6 points in the change in score between groups, with a significance level (alpha or probability of type 1 error) of 0.02 for a three-way comparison, a total of 156 patients (52 per group) were required. A potential 15% contingency in recruitment was allowed to cover unplanned withdrawals, requiring an additional 7 patients per arm for a total of n=177.

3.2.8 Trial measurements and blinding

An overview of all trial measurements and time-points is given in **Table 3.2**. Neither the author, as Principal Investigator or patients was blinded to the intervention group allocation. However, extraction of data from 7-day food diaries was performed by research personnel blinded to the patients' trial group allocation.

A Case Report Form (CRF) detailing the set of measurements to be collected at baseline, weekly during treatment, on completion of treatment and at one year post treatment was developed to ensure systematic capture of all trial outcome data. A Cost Questionnaire detailing health economic data to be captured at each time-point accompanied the CRF. Data from this questionnaire is currently being analysed and will not be reported in this thesis.

Table 3.2 Schedule of trial measurements

Measurement	Baseline (Start-RT)	Weekly (on-treatment)	Completion (End-RT)	Post-RT (One year)
Toxicity measurements				
IBDQ	√	√	√	√
IBDQ-B	√	√	√	√
Bristol Stool Chart	√	√	√	
Stool sample (SCFA)	√		√	
Nutritional measurements				
Weight, Height	√		√	
Body Mass Index	√		√	
7-Day Food Diary	√		√	
24 hour Recall		√		
Health economic measurements				
Symptom costs		√		
Medication costs		√		
Employment costs		√		
Travel costs		√		
AHP contact hours		√	√	
Interventional measurements (intervention groups only)				
Daily fibre intake (Fibre Points Diary)	√	√	√	
Palatability of intervention (VAS)			√	
Costs of compliance with intervention			√	
Ease of Use of interventional tools (Questionnaire)			√	

3.2.9 Recruitment sites and resourcing

The trial was initially planned as a single centre trial with recruitment to take place at the Fulham Road (London) and Sutton (Surrey) sites of Royal Marsden NHS Foundation Trust.

In September 2011 the fibre study was extended to a second site, the Royal Surrey County Hospital (RSCH) Guildford to increase the pool of eligible patients. Recruitment at RSCH was done primarily by the author with assistance from local clinicians and registered dietitians who had undertaken GCP training.

3.3 Clinical trial: procedures

3.3.1 Ethical approval and trial registration

Examples of documentation associated with trial governance including the Patient Information Sheet, GP letter, Consent Form, Case Report Form (CRF) and Cost Questionnaire are given in **Appendix 2**. A research protocol was developed by the author and submitted for review and scientific scrutiny by the Committee for Clinical Research (CCR) at The Royal Marsden NHS Foundation Trust. Following CCR approval, the trial was registered on-line using the NHS Integrated Research Administration System (IRAS) and submitted to the Local Research Ethics Committee (LREC) for approval.

3.3.2 Governance

Procedures covering all aspects of the trial including patient screening, obtaining consent and reporting of adverse events complied with Good Clinical Practice (GCP)[236] and guidelines for non-Clinical Trial Investigative Medicinal Products (non-CTIMP) studies. The collection and reporting of trial data including patient follow-up, reasons for drop-out and withdrawal complied with CONSORT recommendations[237]. Overall trial conduct was in compliance with the relevant Royal Marsden NHS Foundation Trust Standard Operational Policies (SOPs).

A Trial Steering Committee was convened and met at least quarterly to review trial progress, operational issues and adverse events. These meetings were attended by the author, the Chief and Co-investigators, statisticians and a patient representative. Any trial personnel with 'patient contact' (including taking consent) were required to have completed GCP training not longer than two years prior to the date of taking a patient consent.

The author, as Principal Investigator was responsible for all operational activities including patient screening, invitation, taking consent, obtaining trial measurements, reporting trial withdrawal and adverse events, capture and secure transfer of data and attending to daily operational queries from patients, clinicians and radiographers regarding trial participation.

3.3.3 Patient identification and screening

Potentially eligible patients were identified from lists of new patients for pelvic radiotherapy presented at audit and from relevant new patient clinic lists. Each patient was given a unique (tracking) identifier, comprising sequential number and responsible consultant initials, and entered in a recruitment log to which only the author and trial Data Administrator had access. Screening outcomes (i.e. 'missed'; 'accepted'; declined'; 'excluded') and reasons why, were captured to allow analysis of recruitment trends and reasons for declining trial entry.

3.3.4 Initial invitation to the trial

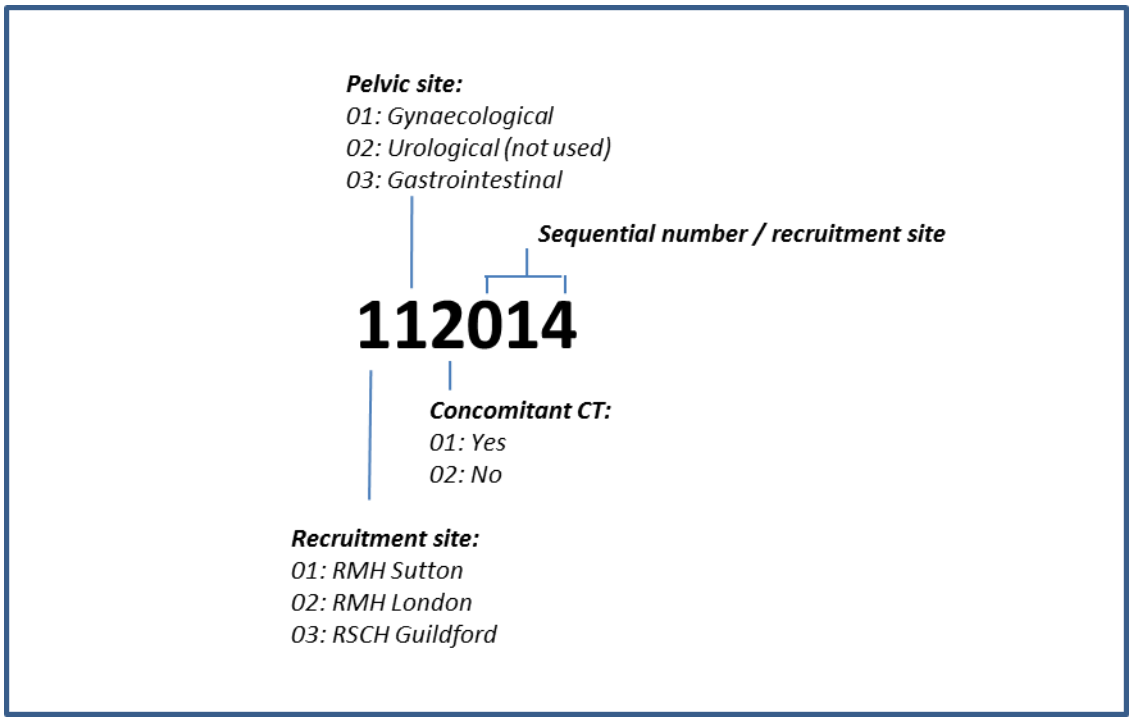
If possible, patients were invited to the trial at their radiotherapy planning scan and if agreeable, given a Patient Information Sheet. Patients not seen at radiotherapy planning were contacted by telephone and sent a Patient Information Sheet. All patients were invited to contact the Principal Investigator or Chief Investigators with any questions or queries. At least 24 hours was required to have elapsed between receipt of Information Sheet by the patient and acceptance or refusal of trial entry.

3.3.5 Obtaining consent and randomisation

Consenting patients completed and signed a consent form which was witnessed by the author as Principal Investigator. An original copy of the consent form was filed in the patient's trial file and a copy given to the patient if requested. With the patient's consent, their General Practitioner was informed in writing of trial participation, using a standard letter approved by the research and ethics committees.

Patients were randomised to the trial by the Institute of Cancer Research (ICR) randomisation office using the minimisation method and allocated one of three trial groups, stratified for concomitant chemotherapy (yes or no) and for pelvic site (gynaecological or gastrointestinal) and given a 6-digit trial identifier (**Figure 3.2**). Patients' radiotherapy treatment sheets were annotated with randomisation group and date of trial entry.

Figure 3.2 The patient identifier (trial number)



3.3.6 Trial withdrawal and adverse events

Patients were withdrawn from the trial if they expressed a wish to withdraw or if they experienced toxicity that necessitated permanent cessation of their radiotherapy, precluded oral intake or required surgical intervention. Reasons for withdrawal were captured in the trial database.

Patients were assured that trial withdrawal would not affect their standard medical care. Adverse events were reported in accordance with local (RMH) Standard Operating Procedures.

3.4 Clinical trial: measurements

3.4.1 Nutritional outcomes

Nutritional status was measured at start and end of radiotherapy using weight, height and BMI. Patients recorded their nutritional intake during the first and last week of radiotherapy using a 7-day un-weighed, food diary. Once per week during radiotherapy, nutritional intake was assessed using the 24 hour recall method and dietary advice provided to help patients comply with fibre target.

At these weekly meetings, for those in the high and low fibre groups, self-reported compliance with target fibre intake was assessed with reference to the patient's exchange diary. Palatability of intervention was assessed using a simple visual analogue scale designed for the trial.

3.4.1.1 Height

Height was measured using a stadiometer attached to electronic Seca weighing scales (Marsden, Oxon, UK). Patients were measured without shoes, standing straight with head in the Frankfurt plane. Height was recorded in centimetres, to one decimal place.

3.4.1.2 Weight

Patients were asked to remove outdoor clothing, heavy pocket contents and shoes before stepping onto electronic Seca column scales (Marsden, Oxon, UK). Weight was recorded in kilograms to the nearest 0.1 Kg. Hospital scales are calibrated annually by an independent contractor and must to conform to relevant weights and measures legislation.

3.4.1.3 Body Mass Index (BMI)

Body Mass Index, a measure of appropriateness of weight in relation to height, was calculated using the equation: BMI (Kg/m^2) = Weight (Kg) / [Height (m)]^2. Interpretation of BMI was as follows: < 16: severely underweight; 16-18.5: underweight; 18.5-25: normal range; 25-30: overweight; 30-40: obese; > 40 morbidly obese.

3.4.1.4 Estimated nutritional and fibre intake (7-Day food diaries)

The 7-day food diary was completed by patients in all trial groups. This method was chose for estimation since intake values for individual nutrients using this method has been shown to correlate more closely than any other method with 16-day weighed records[238]. The 7-D diary, available in A5 or A4 size, comprised two-pages per intake day and included advice on how to estimate portion sizes using standard household

measures. It also included a brief questionnaire detailing preferred choices in terms of size and type (or brand) of commonly consumed items (e.g. milk, bread).

Patients were advised that there was no need to weigh items unless they had difficulty estimating portion sizes. However, they were encouraged to note the weight of consumed pre-packaged items. Data from the 7-day food diaries was entered into DietPlan dietary analysis software, Forestfield, Horsham, UK, v.6.70 by two investigators trained by the author in the use of the software. Diary items were entered with reference to UK standard portion sizes[239] and food databases: UK Composition of Foods IDS 3424; UK Nutrient Databank 5934, supplemented by specialist databases as required.

An aggregated (day-by-day) method of analysis was chosen which allowed for the future analysis of nutritional intake on an averaged basis for any combination or number of days. It was anticipated that this method would enable future examination of recording fatigue of patients participating in nutritional research studies. Fibre (NSP Englyst method) and macronutrient intake was analysed at start and end of radiotherapy.

3.4.1.5 Compliance with target fibre intake

The measurement of compliance with target fibre intake was considered to be a key aspect of the trial and one which is often overlooked. Percentage cut-offs were developed (**Table 3.3**) so that, for example, a patient in the high fibre group achieving an average daily intake of 14.4g NSP / day would be considered at least 80% compliant with the target intervention for this group of 18 g NSP / day.

Table 3.3 Cut-offs for assessment of compliance

Trial Group	80%	85%	90%	100%
High fibre, g/d NSP	>14.39	>15.29	>16.19	>17.99
Low fibre, g/d NSP	<12.01	<11.51	<11.01	<10.01

3.4.1.6 Recalled intake (24 hour recall)

At weekly intervals during radiotherapy, patients were asked to recall all food and drink consumed on the previous day using the 24 hour recall method and were encouraged to think of items consumed in sequence from waking until bed-time. Prompting from the author was done to clarify items consumed which may have contributed to fibre intake. Discussion regarding intake also served to reinforce standard dietary advice for those in the control group and for those in the high or low fibre groups was a useful opportunity to informally assess compliance with fibre target in conjunction with the exchange diary. The 24-hour recall data was not used as a primary nutritional outcome measure.

3.4.1.7 Ease of use of the Fibre in Foods guidance booklet

A questionnaire assessing the ease of use of the "Fibre in Foods" booklet was developed and given to a sample of patients in the interventional groups. Results were collated and expressed using descriptive techniques.

3.4.1.8 Quality of Life (IBDQ score)

The entire 32 question IBDQ questionnaire was used to assess change in quality of life indices between start and end of radiotherapy. Change between baseline and nadir score was also calculated. Mean difference in IBDQ score change between groups was analysed for significance.

3.4.2 Toxicity outcomes

All toxicity outcome tools (including the RTOG scoring tool for reference) and a copy of the patient instructions for the collection of faecal sample for SCFA analysis are given in **Appendix 3**. The primary toxicity endpoint for the trial was the difference in the change (fall) in IBDQ-B score between groups from start of radiotherapy to nadir (worst) score during treatment.

3.4.2.1 Inflammatory Bowel Disease Questionnaire – Bowel subset score (IBDQ-B)

IBDQ-B scores were assessed weekly during radiotherapy. Cumulative acute toxicity scores using the Area Under the Curve (AUC) method were also computed as these may be important predictors of longer-term outcomes[46 47].

Weekly scores were transformed by subtraction from the maximum score attainable: 70. Transformed scores were then summed as follows: [0.5 * baseline + sum of interim acute scores + 0.5 * final score] and the relationship between acute_ IBDQ-B_AUC and occurrence of late toxicity was explored.

3.4.2.2 Stool output parameters (Bristol Stool Form scale)

The Bristol Stool Form scale (usually referred to as the Bristol Stool Chart) was used to assess change in stool characteristics during treatment and was completed by patients in all trial groups. The tool is an accepted method for measurement of stool form[240] and comprises 7 stool forms ranging from type 1: 'separate hard lumps, like nuts, hard to pass' to type 7: 'watery, no solid pieces, entirely liquid'.

At our institution, the scale is embedded within the Royal Marsden Stool Chart, which allows for the recording of daily stool output or frequency. Previous studies from our group had shown this to be a feasible patient-completed tool for toxicity measurement in this setting[75] although surprisingly there is still no one single accepted definition of diarrhoea in this or any other clinical setting.

Patients (all groups) were coached in the interpretation of stool forms and asked to make daily entries in their stool chart from day one to final day of radiotherapy. The complete set of patient-reported data captured in the chart included: details of every bowel opening event / day (frequency); time of bowel opening event; stool form for each event (consistency); presence of blood in stool (yes / no); presence of mucus in stool (yes / no) and use of anti-diarrhoeal medication.

On return of the BSF scale to the author, data was extracted and summarised into excel spreadsheets to allow calculation of the following variables: mean weekly stool frequency; number of days per week on which anti-diarrhoeal medication was used; mean weekly stool form and number of days per week on which a stool form of type 6 or 7 was experienced.

3.4.2.3 Faecal Short Chain Fatty Acids (SCFA)

Faecal samples were obtained from patients at the start and end of radiotherapy. A stool collection kit was provided with instructions. On receipt of returned stool sample 5–10 g were decanted in one of three 15 ml collection tubes. Time since evacuation was recorded. Two tubes for future lyophilisation (freeze drying for correction of water content) were weighed empty and then with stool sample (lids removed in both cases) and then immediately frozen at -80 C. A further 5 grams of stool sample was decanted into a third collection tube and stored at -20 C for future analysis of SCFA concentrations. Weights were recorded to three decimal places. Storage freezers were located in a secure, alarmed, controlled access, tissue bank facility at RMH, Sutton.

On trial completion, freeze drying and analysis of SCFA was conducted in batches with assistance from Ms Rosie Colakatsia (lyophilisation) and Mr Robert Gray (SCFA analysis) both of King's College, London. Samples were transferred on dry ice to the laboratory of Professor Kevin Whelan at King's College London for analysis by the author. Stool samples were placed in batch in a freeze dryer with separation of duplicates into different batches. Samples were dried in vacuum conditions at -47^{o}C and weighed every 4 days until a stable weight (to within 0.01 of the previously obtained weight) was achieved. Mean water percentage and sample dry weights were calculated. This allowed calculation of SCFA concentration per gram of (wet) stool and also per gram of dry stool to account for confounding from stool dilution in those patients with diarrhoea.

Samples for analysis of SCFA were defrosted and 3 -5 g weighed into a stomacher bag for SCFA extraction. Weight of sample in stomacher bag was noted and SCFA extraction buffer comprising 1% H_2PO_4 (Merck, Germany) 0.1% $HgCl_2$ (Sigma, UK) to prevent further fermentation and a synthetic SCFA not metabolised by human gut microbiota, 2,2-dimethylbutyric acid (Sigma, UK) as an internal standard, added in 1:4 dilution. The sample was then homogenised in a stomacher (Seward Stomacher 80) for one minute per side to extract SCFA. Immediately following, 5 ml of faecal slurry was extracted into a Flacon tube for centrifugation. Samples were centrifuged (Beckman GS6R Centrifuge) at 5,000 g, 4^{o}C for 20 minutes.

Following centrifugation, 1 ml of supernatant was filtered through a sterile 0.2µm filter to remove bacteria and aliquoted into a Gas Liquid Chromatography (GLC) compatible 300 µm polypropylene snap ring microvial. Prepared sample vials were analysed in pairs (i.e. baseline and end of radiotherapy) and loaded into a 7890A Aligent Technology GLC system.

Extracted SCFA (0.2 µl aliquot from each sample) were automatically injected splitless into GLC machine equipped with a 220 µm internal diameter, 25 m fused silica capillary column with a film thickness of 0.25 µm (ID-BP21, SGE, Australia). The oven was programmed with an initial temperature of 80°C, which was increased by 10°C/ min up to 145°C, and then 100°C/ min up to 200°C to complete the elution. Each sample was followed by an injection of 1.2% formic acid cleaning solution (Merck, Germany) to minimise carry over from the previous sample.

All chromatograms were integrated on Agilent Chromatogram database (Agilent Technologies, US) running on Windows NT (Microsoft, US). The GC was calibrated with a blend of pure SCFA solutions at 6 different concentrations to produce area: concentration using linear regression from the calibration curves. Concentrations of acetic (2C), propionic (3C), butyric (4C), valeric (5C), isobutyric (4C branched) and isovaleric (5C branched) SCFA were obtained as µmol / g of wet faeces and converted to µmol / g of dry faces using percentage dry weights obtained in lyophilisation.

3.5 Statistical methods and data analysis

A Statistical Analysis Plan (SAP) was written by the author and approved by the Trial Chief Investigator (**Appendix 4**). Statistical analysis was performed in conjunction with the Research Unit's Statistician at the Royal Marsden NHS Foundation Trust. Data was imported to SPSS v.22 for the statistical analysis. Statistical significance was set at $p<0.05$, except for three-way comparisons not using ANOVA techniques or multiple comparisons where it was set at $p<0.025$ or $p<0.0125$, where 'p' represents the probability of that result being obtained under the null hypothesis.

All data was firstly checked for normality of distribution and parametric or non-parametric tests conducted accordingly. Quality control of all trial measurement data was performed by the trial's Data Manager at the Royal Marsden NHS Foundation Trust, London.

Analysis of trial recruitment data including number of patients screened, excluded, missed, invited, declined and withdrawn at each time-point was undertaken and presented using descriptive techniques in accordance with CONSORT requirements[237]. The reasons for exclusion and declining trial entry were pre-defined at trial outset and captured for each patient. The trial recruitment rate was defined as: [number of patients recruited] / [number of patients invited].

Inter-researcher variability in the extraction of data from the 7-day food diaries was conducted since two independent researchers, blinded to trial intervention, had extracted diary data. A total of 18 end-of-treatment 7-day food diaries were randomly selected comprising six diaries per trial group. The estimation of fibre and energy intake by these two researchers was then compared to a gold standard (the author, 'LW'), who, also blinded to trial group allocation and patient identity, analysed the same 18 diaries. A non-significant value ($p>0.05$) for a three-way ANOVA comparison of estimation of fibre or energy intake between investigators was deemed to be indicative of no significant difference between the researchers in their estimation of these two nutritional outcomes.

CHAPTER 4

A randomised controlled trial to investigate the role of low or high fibre diets in patients undergoing pelvic radiotherapy:

Clinical Findings

4.1 Trial performance

4.1.1 Recruitment

The randomised controlled trial opened in October 2010 and closed to recruitment in December 2013 following the recruitment of 166 patients. Originally powered for 156 patients in total, a potential contingency of 7 patients per trial group was planned to allow for withdrawals and attrition of data, making a total of 177 patients. However, as the required data to satisfy the primary endpoint had been successfully captured at the recruitment of 166 patients, the trial was closed at this point to further patients.

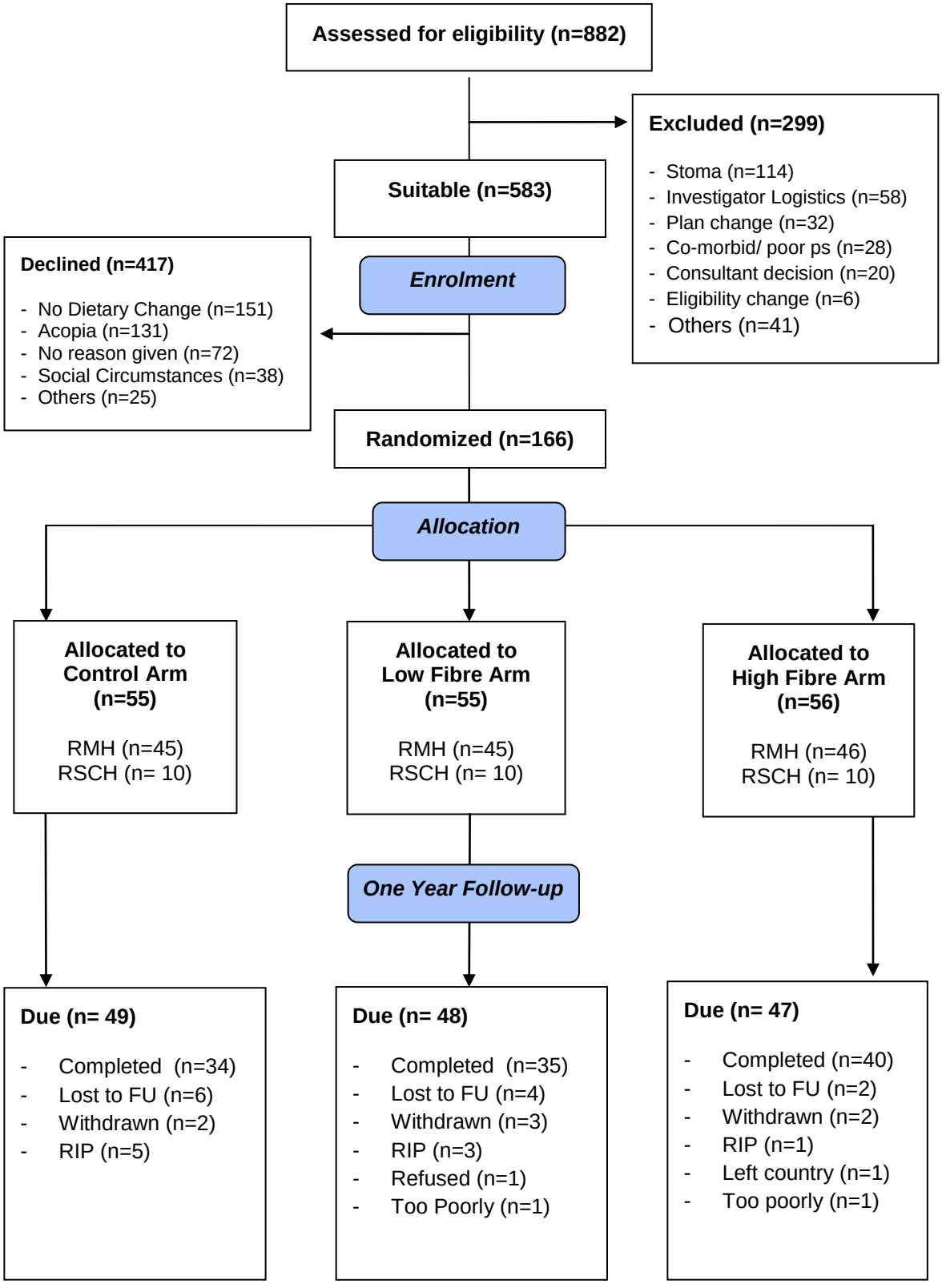
Between October 2010 and December 2013 a total of 882 patients were screened for eligibility to the trial with 583 patients being suitable for invitation. Of the 166 patients randomized to the trial, 55 patients were allocated to the Control group, 55 to the Low Fibre group and 56 to the High Fibre group. A total of 136 patients were recruited at The Royal Marsden NHS Foundation (RMH), London and Sutton sites and 30 patients at the Royal Surrey County Hospital in Guildford (RSCH).

The trial is currently in the one year follow-up phase with 109 patients of 144 patients available for follow-up having completed their one year measurements (return rate: 79%) leaving a further 35 patients to be contacted.

Of those suitable, 417 patients declined trial entry and 166 agreed to participate representing a recruitment rate of 28%. Of those who declined trial entry, reluctance to adopt a possible change in diet was given as the major reason for refusal (36%) followed by ‘cannot cope’ with the demands of the trial in addition to radiotherapy treatment (31%).

By far the major reason for exclusion in those screened was presence of a stoma (38%) which was a stated exclusion criterion. Trial data in compliance with CONSORT requirements are shown in **Figure 4.1.**

Figure 4.1 Trial CONSORT diagram depicting current trial status



4.1.2 Baseline characteristics

Of the 166 patients randomised to the trial, the median (range) age of the cohort was 62.5 years (26 – 91) of whom 42% were male (**Table 4.1**). Sixty four percent had gastrointestinal and 36% gynaecological cancers. Seventy two percent of patients received concomitant chemotherapy. Median radiotherapy dose was 50.4 Gray over a modal treatment period of 28 treatment days (equating to 5.5 weeks).

Table 4.1 Baseline characteristics of randomised patients (n=166)

Characteristic	Control n=55	Low Fibre n=55	High Fibre n=56	All groups n=166	P value
Age: years Median (range)	63 (35 – 88)	62 (26 – 91)	64 (28 – 87)	62.5 (26 – 91)	0.959*
Gender: n (%) Male Female	23 (42) 32 (58)	26 (47) 29 (53)	21 (37) 35 (63)	70 (42) 96 (58)	0.580**
Pelvic site: n (%) Gastrointestinal Gynaecological	35 (64) 20 (36)	36 (65) 19 (35)	35 (63) 21 (37)	106 (64) 60 (36)	0.948**
Concomitant CT: n (%) No Yes	17 (31) 38 (69)	14 (25) 41 (75)	15 (25) 42 (75)	46 (28) 121 (72)	0.739**
RT dose (Gy): Median (range)	52.2 (45.0 – 70.0)	50.4 (30.0 – 59.4)	50.4 (45.0 – 69.6)	50.4 (30.0 – 70.0)	0.398*

Key: CT: chemotherapy, *significant: p<0.05, *Kruskal-Wallis' test, **Chi-squared test

Trial groups were comparable at baseline; p values are all >0.05 for each group-wise comparison indicating no significant differences between groups in major demographic and oncological variables (**Table 4.1**).

Anatomical sites for gynaecological and gastrointestinal cancers are given in **Table 4.2**.

Table 4.2 Gynaecological and gastrointestinal cancers: anatomical sites

Characteristic	Control n=55	Low Fibre n=55	High Fibre n=56	All groups n=166
Gynaecological:	20	19	21	60 (36)
Endometrial	13 (65)	14 (74)	9 (43)	36 (60)
Cervical	4 (20)	5 (26)	11 (52)	20 (33)
Vagina	2 (10)	0	1 (5)	3 (5)
Vulva	1 (5)	0	0	1 (2)
Gastrointestinal:	35	36	35	106 (64)
Colorectal	27 (77)	27 (75)	26 (74)	80 (75)
Anal	8 (23)	9 (25)	9 (26)	26 (25)

4.1.3 Withdrawn patients

Seven patients were withdrawn from the trial immediately after randomisation (n=4) or during the trial (n=3) and their data excluded from further analysis. The characteristics of withdrawn patients were: median (range) age: 53 years (39 – 67); males: 3; females: 4; gastrointestinal cancers: 6; gynaecological cancers: 1.

Reasons for withdrawal and allocated trial groups at randomisation were: declined to commence intervention following randomisation: 2 (Low fibre); stoma placed prior to treatment: 2 (control: 1, high fibre: 1); hospitalization and cessation of radiotherapy: 2 (control: 1, low fibre: 1); plan change resulting in no radiotherapy treatment: 1 (high fibre).

4.1.4 Evaluable data

4.1.4.1 Summary of data obtained

Following exclusion of data from the seven withdrawn patients, 159 patients completed the acute phase of the trial and provided evaluable data. A summary of the evaluable data items obtained for the trial's primary and secondary end-points shown in **Table 4.3**.

Table 4.3 Evaluable data from the randomised controlled trial (total n=159)

Time point	Control n=53	Low fibre n=52	High fibre n=54	% Return* All groups
IBDQ-B (Primary Outcome)				
Baseline (start of radiotherapy)	53	52	54	100
End of radiotherapy	53	52	54	100
IBDQ (Quality of Life)				
Baseline (start of radiotherapy)	53	52	54	100
End of radiotherapy	53	52	54	100
Bristol Stool Chart				
Completed charts returned	44	39	42	79
Faecal samples obtained for SCFA analysis				
Number of paired samples returned	16	15	10	26
Weight (kg)				
Baseline (start of radiotherapy)	53	52	54	100
End of radiotherapy	53	52	54	100
BMI (kg/m^2)				
Baseline (start of radiotherapy)	53	52	54	100
End of radiotherapy	53	52	54	100
7 Day Food Diaries				
Baseline (start of radiotherapy)	51	47	48	92
End of radiotherapy	44	41	43	81
Number of paired diaries returned	44	41	42	127
Fibre Exchange Diaries				
Completed diaries returned	NA	34	36	66
Ease of Use of Fibre in Foods booklet questionnaire				
Number completed	NA	22	22	NA
Weekly 24 Hour Recalls				
Number completed in total	102	107	103	312
Average number completed per group	1.9	2.1	1.9	2.0
Visual Analogue Scales (palatability of trial diet)				
Number completed	NA	40	38	74

Key: * Percentage return calculated on basis of n=159 (all groups) or n=106 (low and high fibre groups).

4.1.4.2 Completeness of primary endpoint: IBDQ-B scores

Primary endpoint data, IBDQ-B scores, were obtained from 159 patients at baseline. Baseline equated to start of radiotherapy. A baseline IBDQ-B score was defined as one obtained on day one of radiotherapy or within five days of start of radiotherapy. Four patients, who were unable to complete the IBDQ during their first radiotherapy treatment, returned completed questionnaires within five days of the start of radiotherapy and these were treated as baseline scores.

A final 'end of radiotherapy' time-point was created for each patient to enable statistical comparison. Missing end of radiotherapy scores were carried forward from the last available score provided it was within one week of their last radiotherapy treatment fraction (occurred for n=8 patients).

4.1.4.3 Quality of Life endpoint data: IBDQ scores

Quality of life data, IBDQ scores were obtained from the same number of patients as those providing IBDQ-B scores. Baseline scores were obtained for 159 patients on day one of radiotherapy and a further four patients provided a score within five days of the start of treatment. Final, end of radiotherapy scores were not available for eight patients on the last day of treatment and their IBDQ score for the immediately preceding week was carried forward.

4.1.4.4 Secondary toxicity endpoint data: stool charts and faecal samples

Of the secondary toxicity endpoints 125/159 (79%) patients returned completed stool charts, representing a total of approximately 4340 recording days, estimated on the basis of an average five week course of treatment. However, not all patients completed stool details for all weeks of radiotherapy.

The total number of completed weeks of stool data and the number per trial group for each week of treatment was as follows: week 1 of radiotherapy: n=125 (control: 44; low fibre: 39; high fibre: 42), treatment week 2: n=122 (control: 43; low fibre: 38; high fibre: 41), treatment week 3: n=123 (control: 43; low fibre: 39; high fibre: 41), treatment week 4: n=123 (control: 44; low fibre: 39; high fibre: 40), treatment week 5: n=104 (control: 37; low fibre: 30; high fibre: 37) and treatment week 6: n=39 (control:

14; low fibre: 11; high fibre: 14). The number of stool charts obtained fell in week 6 due to fewer patients remaining on treatment.

Patients receiving treatment at the Royal Marsden NHS Foundation Trust were invited to provide a stool sample at baseline and the end of radiotherapy. Patients recruited at The Royal Surry County Hospital were not invited to provide stool samples as the second site approval did not extend to the collection of human tissue. Sixty patients provided stool samples at baseline and 42 provided samples at end of radiotherapy. Of these a total of 41 paired (i.e. baseline and end of radiotherapy) samples were obtained.

All patients were invited to provide a stool sample. However, only a small percentage of those who took home a stool collection kit actually returned samples. Further, only 68% (41/60) of those who provided baseline samples also provided one at the end of radiotherapy. Reasons for non-return of stool samples were not captured. However, many patients expressed regret that they were unable to do this and cited fatigue or loose, frequent and small quantities of stool that were difficult or unpleasant to collect.

4.1.5 Analysis of reasons for declining trial entry

An analysis of 417 patients (missing data: 20) who declined trial entry reveals the most frequently cited reason by females (both hospital sites) for declining trial entry was ‘no dietary change’, whilst that for males was ‘cannot cope’.

Table 4.4 Characteristics of patients who declined trial entry

Site: RMH (n=333) Missing data for n=20	**Reasons for decline (n=417)**				
	Cannot cope n=96	**No dietary change n=110**	**No reason given n=65**	**Social circumstances n=34**	**Other reasons n=28**
Age: mean (sd)	65.1 (12.6)	63.0 (12.9)	65.0 (13.1)	66.2 (12.3)	65.6 (13.6)
Males : Females	27 : 69	25 : 85	20 :45	15 : 19	14 : 14
Site: RSCH (n=60) Missing data for n=0	**Cannot cope n=24**	**No dietary change n=20**	**No reason given n=8**	**Social circumstances n=2**	**Other reasons n=6**
Age: mean (sd)	70.2 (11.2)	58.6 (12.2)	56.8 (5.5)	66.5 (3.5)	65.5 (14.5)
Males : Females	4 : 20	4 : 16	1 : 7	1 : 1	2 : 4
Total combined sites (n=393) Missing data for n=20	**Cannot cope n=120**	**No dietary change n=130**	**No reason given n=73**	**Social circumstances n=36**	**Other reasons n=34**
Age: mean (sd)	66.1 (12.5)	62.3 (12.8)	64.1 (12.7)	66.2 (12.0)	65.6 (13.5)
Males : Females (n) Males : Females (%)	31 : 89 27 : 32	29 : 101 26 : 36	21 : 52 19 : 19	16 : 20 14 : 7	16 : 18 14 : 6
Total no. males declining	**All reasons 113 / 393**				
Total no. females declining	**All reasons 280 / 393**				

Key: RMH: Royal Marsden NHS Foundation Trust (Sutton, Surrey and London), RSCH: Royal Surrey County Hospital, Guildford.

4.1.6 Adverse events

Four adverse events were reported due to admission to hospital for symptom control. No adverse effects were reported that were related to the trial diet and no patients withdrew citing reasons related to the intervention.

4.2 Trial results: presentation

Trial findings are presented in two chapters. **Chapter 4** contains the clinical findings, **Chapter 5**, presents the nutritional findings and aims to provide nutritional insight into the findings presented in the current chapter. Each has a concluding discussion highlighting the main findings and indicating their possible importance.

The clinical findings begin with an analysis of the trial's primary trial endpoint (IBDQ-B). The findings then continue with further analysis of gastrointestinal symptoms, stool characteristics, faecal short chain fatty acids and quality of life (IBDQ).

The following conventions are used in the presentation of trial results. Negative values for a change in IBDQ-B and IBDQ scores between time-points indicate a fall in score and thus worsening symptoms.

For statistical analyses, where one way ANOVA has been performed, the data has been assessed for normality and found to be acceptable to consider as normally distributed. Non-normally distributed data are analysed using an appropriate non-parametric test.

4.3 Gastrointestinal symptom scores (IBDQ-B)

The IBDQ-B tool was used to assess gastrointestinal symptoms. The primary, powered endpoint of the trial was difference between groups in the change in IBDQ-B scores between the acute time-points baseline (start of radiotherapy) and nadir (worst on treatment score).

4.3.1 Scores at acute time-points

The mean (sd) IBDQ-B scores at acute time-points: baseline, end of radiotherapy and nadir (lowest on-treatment) are given in **Table 4.5**.

Table 4.5 IBDQ-B scores at specific time-points

IBDQ-B Variable	Time-point	Control n=53	Low fibre n=52	High fibre n=54	*ANOVA p value*
		IBDQ-B score: Mean (sd)			
IBDQ-B Baseline score	Start of RT	64.4 (6.7)	63.9 (9.4)	61.70 (9.7)	0.240
IBDQ-B Nadir score	Lowest on-treatment	48.9 (12.8)	52.1 (10.6)	51.5 (11.6)	0.331
IBDQ-B End RT score	End of RT	53.6 (13.0)	56.5 (10.9)	58.6 (10.5)	0.081

A one way ANOVA indicated that there was no significant difference between groups in scores at baseline, on-treatment nadir (worst) or end of radiotherapy ($p>0.05$ for all comparisons).

4.3.2 Change in scores between time-points

The primary endpoint for the trial was the difference between groups in the change in IBDQ-B scores between baseline and nadir (worst) score during radiotherapy.

A one way ANOVA (**Table 4.6**) revealed no significant differences between groups (p=0.093) in the change in score between baseline and nadir. Although not statistically significant, the control group exhibits the greatest fall in score between baseline and nadir (-15.5 points) in comparison to the high fibre group (-10.2 points).

Table 4.6 Change in IBDQ-B scores between time-points

IBDQ-B Variable Mean (sd)	**Time-point**	**Control n=53**	**Low fibre n=52**	**High fibre n=54**	***ANOVA p value***
Change in IBDQ-B score: Mean (sd)					
IBDQ-B Nadir change	Baseline to Nadir	-15.5 (13.4)	-11.8 (10.7)	-10.2 (13.7)	0.093
IBDQ-B End RT change	Baseline to end-RT	-10.8 (13.6)	-7.4 (11.6)	-3.1 (13.0)	**0.009***

Key: Negative values represent a fall in score (worsening symptoms)

A secondary endpoint was the difference between groups in the change in IBDQ-B scores between baseline and end of radiotherapy. The results of this analysis are also given in **Table 4.6**. A significant difference between groups was identified (p=0.009).

Post-hoc, pair-wise, comparison between groups (Bonferroni method) identified a significant difference (p=0.007) of 7.7 points between the control and high fibre groups (**Table 4.7**) in favour of the high fibre group resulting in a smaller fall in IBDQ-B score.

Table 4.7 Post-hoc analysis: difference in the change in IBDQ-B score

Group (i)	Group (ii)	Mean Difference (Grp I *v* Grp 2)	95% Confidence Interval		p value
			Lower Bound	Upper Bound	
Control	Low fibre	-3.4	2.7	-9.4	0.535
	High fibre	-7.7	-1.7	-13.7	**0.007***
Low fibre	Control	3.4	9.4	-2.7	0.535
	High fibre	-4.3	1.7	-10.3	0.249
High fibre	Control	7.7	13.7	1.7	**0.007***
	Low fibre	4.3	10.3	-1.7	0.249

Key: Positive values for mean difference favour Group (i), negative values favour Group (ii).
*significant: p<0.05.

In contrast, the difference between the low and high fibre groups, with a mean difference in score of 4.3 points was not significant (p=0.249).

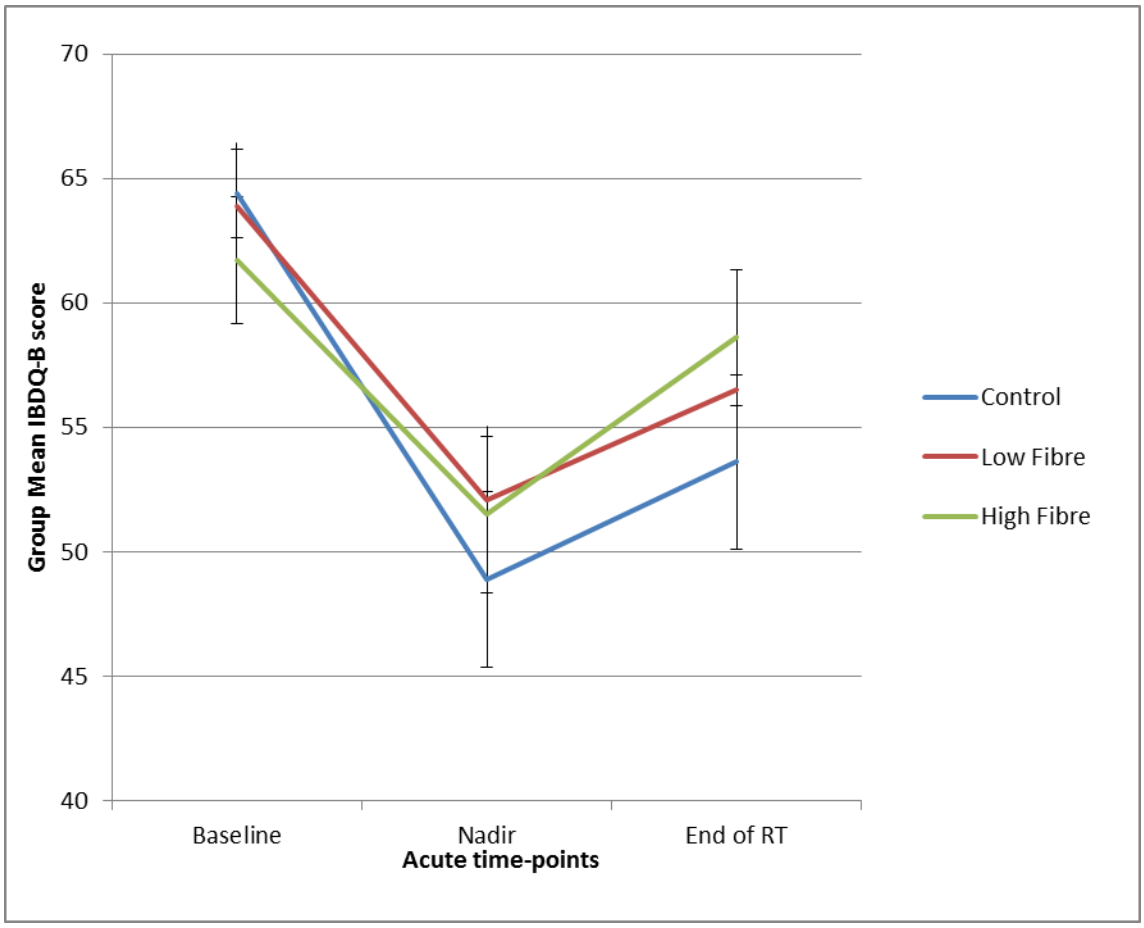
4.3.2.1 Descriptive analysis: change in IBDQ-B score

A graphical representation of the mean group IBDQ-B scores at each acute time-point is given in **Figure 4.2**. For all groups, the scores show some recovery post nadir but do not rebound to reach baseline levels for any group by the radiotherapy end point.

When expressed as a percentage of the maximum possible change in IBDQ-B score between time-points (60 points), the change in score experienced by each group between baseline and nadir was 26% (control), 20% (low fibre) and 17% (high fibre).

The change in score between baseline and end of radiotherapy was 18% (control), 12% (low fibre) and 5% (high fibre). Changes in score of >10% in either direction (i.e. worsening or improving symptoms) are taken to be clinically significant.

Figure 4.2 Change in group mean IBDQ-B scores at acute time-points



Key: Error bars show 1.96*standard error in both directions

4.3.2.2 Change in IBDQ-B AUC score

A further secondary endpoint of the trial was a comparison of the area under the curve (AUC) equating to the total increased symptom burden during treatment. Computation of IBDQ-B AUC values for 153 patients (control: 53; low fibre: 50; high fibre: 50) with a minimum of four consecutive weekly IBDQ-B scores resulted in a median (range) IBDQ-B AUC for the cohort of 41.0 (0 – 179).

No significant difference between groups was found in the acute IBDQ-B AUC (p=0.576) using a Kruskal Wallis' non-parametric test.

4.3.2.3 Exploratory sub-group analysis of IBDQ-B scores by pelvic site

An exploratory sub-group analysis, defined by pelvic site was conducted. However, the study was not powered for this analysis and any statistically significant results must be viewed with caution.

For the 100 patients with gastrointestinal cancers, one way ANOVA revealed no significant differences between groups in IBDQ-B scores at the nadir or at the end of radiotherapy or in the change in score between baseline and these time-points (p>0.05 for all comparisons).

However, in the exploratory sub-group analysis of the 59 patients with gynaecological cancers, a significant difference was identified between groups in IBDQ-B scores at the end of radiotherapy (p=0.010) and in the change in score between groups from baseline to end of radiotherapy (p=0.013) as shown in **Table 4.8**.

Table 4.8 IBDQ-B score and change in score: pelvic sub-group gynaecology

IBDQ-B variable	Time-point	Control n=20	Low fibre n=18	High fibre n=21	*ANOVA p value*
IBDQ-B score: Mean (sd)					
IBDQ-B Baseline score	Start of RT	65.8 (5.2)	66.1 (7.9)	65.0 (6.4)	0.843
IBDQ-B Nadir score	Lowest on-treatment	47.1 (12.6)	53.7 (9.6)	54.0 (9.2)	0.074
IBDQ-B End RT score	End of RT	53.3 (10.8)	58.7 (7.8)	62.4 (8.9)	**0.010***
IBDQ-B Change in score: Mean (sd)					
IBDQ-B Nadir change	Baseline to Nadir	-18.8 (12.9)	-12.4 (7.1)	-11.0 (10.6)	0.054
IBDQ-B End RT change	Baseline to end-RT	-12.6 (10.9)	-7.4 (8.6)	-2.5 (11.4)	**0.013***

Key: Negative values represent a fall in score (worsening symptoms), RT: radiotherapy
*significant: p<0.05

Post-hoc analysis (Bonferroni method) identified a mean difference in score of 9.2 points at the end of radiotherapy between the control and high fibre groups in favour of the high fibre group (p=0.008), but did not find any differences between any other groups. Further post-hoc analysis identified a difference in the change in score of 10.0 points (baseline to end of radiotherapy) between the control and high fibre groups in favour of the high fibre group (p=0.010), but did not find any differences between any other groups.

4.4 Analysis of change in stool characteristics

Changes in stool characteristics including frequency (number of daily bowel-opening events) stool form / consistency (Bristol stool form scale), use of anti-diarrhoeal medication and incidence of loose or unformed stool (stool type 6 or 7) were analysed to identify differences between groups.

These analyses comprised secondary analyses and thus the trial was not powered to detect a difference in any of these outcomes. Statistically significant findings should thus be interpreted with caution. Further, an overall 21% of stool charts were not returned; control group: 83% returned, low fibre: 75% and high fibre: 78%.

4.4.1 Interpretation of stool chart data

For each patient returning a self-completed, or partially self-completed stool chart, mean daily stool frequency per (radiotherapy) week, mean daily stool type per week, number of days use of anti-diarrhoeal medication per week and number of days on which stool type of 6 or 7 was experienced per week were calculated.

Mean weekly stool frequency and mean stool type was calculated for each study group for each week by summing the weekly scores for all patients within the group and calculating the mean value for the group. The number of days on which anti-diarrhoeal medication was used and the incidence of loose stool (number of days on which a stool type of 6 or 7 was experienced) were summed for each patient by treatment week. The average number of days per patient, per week, on which anti-diarrhoeal medication was used, or loose stool experienced, was then calculated for each group by dividing the total number of days on which these events occurred in that week by the number of patients in that group returning data for that week.

An exploratory comparison of the difference between groups in stool frequency and type at week one, week four and end of radiotherapy was conducted. A comparison of the change over time (by treatment week) between groups in use of anti-diarrhoeal medication and incidence of loose stool is presented using descriptive statistics.

4.4.2 Between group differences: stool frequency and type

Stool frequency and stool type data were not normally distributed. Median (range) values and the non-parametric Kruskal Wallis' test was used to compare differences between groups at week one, four and end of radiotherapy. No significant differences were identified (**Table 4.9**).

Table 4.9 Stool frequency and type: between group analysis

Stool characteristic / time-point	**Control**	**Low fibre**	**High fibre**	***Kruskal Wallis' P value***
Median (range) at each time-point				
Stool frequency (bowel movements per week)				
week 1 n	n=43	n=39	n=42	
	1.9 (0.4 – 6.7)	1.7 (0.7 – 12.1)	2.0 (0.7 – 13.9)	0.797
week 4 n	n=44	n=39	n=40	
	2.8 (0.6 – 9.7)	2.6 (0.9 – 13.4)	2.5 (0.6 – 12.6)	0.825
End of RT n	n=41	n=37	n=39	
	3.0 (0.3 – 13.5)	2.7 (0.6 – 11.0)	2.3 (0.9 – 13.8)	0.636
Stool type (average stool type per week)				
week 1 n	n=44	n=39	n=42	
	4.7 (2.0 – 6.4)	5.0 (2.4 – 6.6)	4.9 (1.8 – 6.6)	0.630
week 4 n	n=43	n=38	n=40	
	5.1 (1.3 – 6.8)	5.3 (2.7 – 7.0)	5.2 (1.3 – 6.8)	0.906
End of RT n	n=40	n=37	n=39	
	4.8 (2.5 – 6.8)	5.2 (3.9 – 7.0)	5.1 (3.0 – 6.6)	0.225

4.4.3 Descriptive analysis: use of anti-diarrhoeal medication

The average number of days on which patients used anti-diarrhoeal medication, for each week of treatment is depicted in **Figure 4.3**.

Figure 4.3 Use of anti-diarrhoeal medication

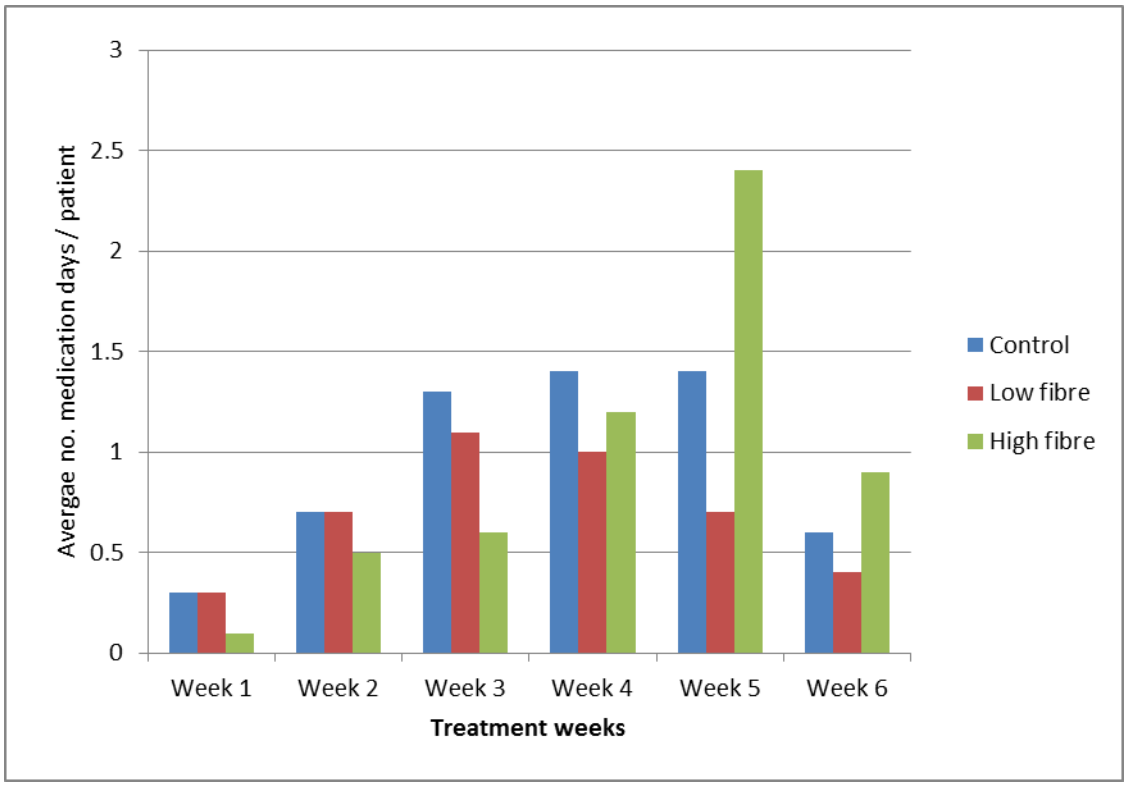


Figure 4.3 illustrates the increasing use of anti-diarrhoeal medication (most commonly Loperamide) as treatment progresses. There is a marked increase in the use of medication in week 5 for the high fibre group in comparison to the control or low fibre groups.

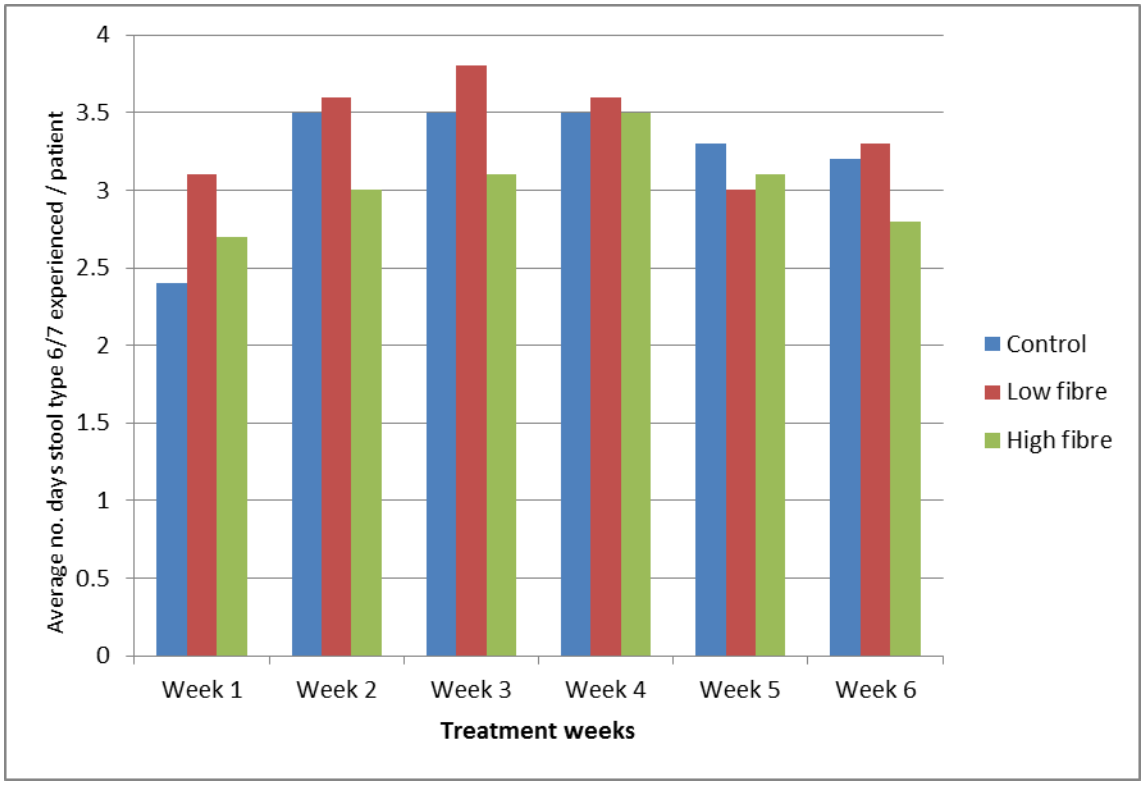
The number of patients remaining on treatment at week six is less than for weeks one to five and thus the data for week six is not necessarily comparable to that obtained in the preceding weeks as group composition will have changed.

4.4.4 Descriptive analysis: incidence of loose stool

The average number of days on which patients experienced loose or unformed stool (Bristol stool type 6 or 7) for each week of treatment is depicted in **Figure 4.4**. The incidence of loose stool is largely comparable across groups for all treatment weeks although the number of days on which loose stool is experienced appears less per patient for the high fibre group for treatment weeks two, three and six compared to the control or low fibre groups.

However, the number of patients remaining on radiotherapy treatment at week six is less than for weeks one to five and thus the data for week six is not necessarily comparable to that obtained in the preceding weeks due to changes in trial group composition.

Figure 4.4 Incidence of loose stool



4.5 Analysis of short-chain fatty acids

Change in the concentrations of individual SCFA (acetate, propionate, butyrate, valerate, iso-butyrate, iso-valerate) and total SCFA were analysed to identify differences between groups. No previous studies have explored the change in SCFA during pelvic radiotherapy and thus both straight (Carbon: 'C') chain (acetate, propionate, butyrate, valerate) and branched chain (isobutyrate, isovalerate) fatty acid concentrations were measured as well at total SCFA as change in specific fatty acid concentrations could not be anticipated. Previous research in IBD patients has reported significant increases in butyrate concentration following fibre supplementation[194 216 241].

Results are expressed as both 'wet' and 'dry' values representing the concentration of SCFA in µmol/g of *wet* or *dry* faeces. Dry values are obtained following freeze drying (lyophilisation) of samples and making a correction (based on the change in sample weight) for stool water content. Both wet and dry values were used as it was unclear which would be preferable. One previous study in IBD patients has reported wet weights[216] two further studies did not define concentrations as being in wet or dry units[194 241].

Statistically significant findings should be viewed with caution as only a very small sample of patients (41/136) provided samples. Further, patients providing samples may have represented a biased group in terms of symptom burden, gender, age or other factors.

The fibre trial was not powered to detect a difference in this outcome measure and with such a small sample, the analysis is extremely exploratory.

4.5.1 Patients providing samples for SCFA analysis

Only 41 patients provided paired faecal samples for the analysis of SCFA at baseline (start of radiotherapy) and end of radiotherapy. Samples were not obtained from patients recruited at the Royal Surrey County Hospital, Guildford.

A total of 16 patients in the control group, 15 in the low fibre group and 10 from the high fibre group provided samples at both time-points (**Table 4.10**).

Table 4.10 Characteristics of patients providing samples for SCFA analysis

Characteristic	Control n=16	Low Fibre n=15	High Fibre n=10
Age: years Mean (sd)	61.9 (11.2)	62.8 (10.5)	65.6 (9.0)
Gender: Male : Female	8 : 8	11 : 4	5 : 5
Pelvic site: Gastrointestinal Gynaecological	11 (69) 5 (31)	12 (80) 3 (20)	9 (90) 1 (10)
Concomitant CT: No Yes	3 (19) 13 (81)	3 (20) 12 (80)	3 (30) 7 (70)

Key: CT: chemotherapy

4.5.2 Between group differences: faecal SCFA concentration

Faecal concentrations and change in concentrations (baseline to end of radiotherapy) for individual and total SCFA are given in **Tables 4.11** (wet faeces values) and **Table 4.12** (dry faeces values).

At baseline (start of radiotherapy) one way ANOVA identified significant differences between groups in the concentration of valerate in *wet* faeces (p=0.042), with post-hoc analysis indicating differences between the control and high fibre groups (p=0.040).

Differences were also identified in the concentration of isobutyrate in *dry* faeces (p=0.029), post hoc analysis indicating the differences were between the control and high fibre groups (p=0.024) and valerate in *dry* faeces (p=0.020) with post hoc analysis indicating the differences were between the control and high fibre groups (p=0.018).

No significant differences were identified between groups in the change in SCFA between baseline and end of radiotherapy (**Table 4.11** and **Table 4.12**).

Table 4.11 SCFA concentrations and change in concentration (stool wet weight) at baseline and end of radiotherapy

	Time-point	Control n=16	Low fibre n=15	High fibre n=10	*ANOVA p value*
Mean (sd) concentration: µmol/g wet faeces					
Acetate	Baseline	8.65 (3.18)	9.64 (3.69)	11.93 (4.88)	0.116
	End of RT	6.92 (2.48)	7.95 (3.51)	9.11 (3.62)	0.240
Propionate	Baseline	2.33 (1.14)	2.47 (1.33)	3.13 (2.08)	0.395
	End of RT	1.67 (0.86)	2.54 (1.36)	2.51 (1.20)	0.076
Butyrate	Baseline	1.54 (0.74)	1.49 (0.74)	2.20 (1.23)	0.113
	End of RT	1.20 (0.66)	1.14 (0.73)	1.48 (1.14)	0.572
Isobutyrate	Baseline	0.30 (0.16)	0.38 (0.18)	0.48 (0.31)	0.114
	End of RT	0.26 (0.12)	0.28 (0.10)	0.30 (0.14)	0.740
Valerate	Baseline	0.14 (0.06)	0.16 (0.08)	0.23 (0.13)	**0.042***
	End of RT	0.12 (0.50)	0.12 (0.07)	0.14 (0.08)	0.662
Isovalerate	Baseline	0.27 (0.12)	0.34 (0.16)	0.40 (0.25)	0.187
	End of RT	0.25 (0.10)	0.35 (0.09)	0.30 (0.14)	0.975
Total SCFA	Baseline	13.2 (4.7)	14.5 (5.4)	18.4 (8.3)	0.110
	End of RT	10.4 (3.9)	12.3 (5.2)	13.8 (5.7)	0.225
Mean (sd) change in concentration: µmol/g wet faeces					
Acetate	Baseline to end RT	-1.73 (3.61)	-1.68 (5.09)	-2.82 (7.44)	0.846
Propionate	Baseline to end RT	-0.67 (1.29)	0.07 (1.41)	-0.62 (1.95)	0.349
Butyrate	Baseline to end RT	-0.34 (0.57)	-0.34 (0.74)	-0.72 (1.89)	0.646
Isobutyrate	Baseline to end RT	-0.03 (0.14)	-0.10 (0.20)	-0.18 (0.29)	0.225
Valerate	Baseline to end RT	-0.02 (0.07)	-0.05 (0.08)	-0.09 (0.15)	0.222
Isovalerate	Baseline to end RT	-0.02 (0.11)	-0.09 (0.17)	-0.15 (0.21)	0.119
Total SCFA	Baseline to end RT	-2.8 (5.12)	-2.19 (7.21)	-4.58 (11.45)	0.750

Key: RT: radiotherapy, *significant: $p<0.05$

Table 4.12 SCFA concentrations and change in concentration (stool dry weight) at baseline and end of radiotherapy

	Time-point	Control n=16	Low fibre n=15	High fibre n=10	*ANOVA p value*
Mean (sd) concentration: µmol/g dry faeces					
Acetate	Baseline	36.0 (18.7)	41.9 (22.7)	50.7 (21.6)	0.229
	End of RT	29.2 (15.0)	40.1 (25.0)	40.1 (16.6)	0.234
Propionate	Baseline	9.9 (7.1)	11.3 (8.3)	13.2 (9.1)	0.609
	End of RT	7.1 (4.7)	13.4 (9.9)	11.6 (7.9)	0.080
Butyrate	Baseline	6.19 (3.34)	6.48 (4.13)	9.79 (6.08)	0.110
	End of RT	4.49 (3.27)	5.61 (3.80)	6.36 (5.57)	0.702
Isobutyrate	Baseline	1.11 (0.48)	1.46 (0.60)	2.04 (1.39)	**0.029***
	End of RT	1.04 (0.39)	1.38 (0.63)	1.21 90.41)	0.183
Valerate	Baseline	0.54 (0.16)	0.66 (0.38)	0.99 (0.58)	**0.020***
	End of RT	0.50 (0.22)	0.56 (0.38)	0.58 (0.34)	0.774
Isovalerate	Baseline	1.01 (0.36)	1.29 (0.46)	1.70 (1.18)	0.050
	End of RT	0.99 (0.35)	1.21 (0.57)	1.00 (0.23)	0.294
Total SCFA	Baseline	54.8 (27.2)	63.1 (33.9)	78.5 (37.0)	0.202
	End of RT	43.8 (22.4)	62.2 (37.2)	60.9 (27.7)	0.184
Mean (sd) change in concentration: µmol/g dry faeces					
Acetate	Baseline to end RT	-6.79 (23.16)	-1.79 (28.04)	-10.63 (34.48)	0.733
Propionate	Baseline to end RT	-2.86 (8.94)	2.10 (8.01)	-1.57 (9.22)	0.278
Isobutyrate	Baseline to end RT	-0.06 (0.56)	-0.08 (0.85)	-0.83 (1.44)	0.099
Butyrate	Baseline to end RT	-1.23 (3.31)	-0.87 (4.35)	-3.44 (8.91)	0.489
Isovalerate	Baseline to end RT	-0.02 (0.43)	-0.08 (0.72)	-0.72 (1.11)	0.060
Valerate	Baseline to end RT	-0.04 (0.32)	-0.10 (0.43)	- 0.4 (0.68)	0.156
Total SCFA	Baseline to end RT	-11.0 (34.6)	-0.84 (40.5)	-17.6 (52.7)	0.599

Key: RT: radiotherapy, *significant: $p<0.05$

4.5.3 Within group differences: faecal SCFA concentration

Paired t-tests were used to detect within group differences in SCFA concentrations between baseline and end of radiotherapy. The analysis, using the paired concentrations for dry faeces identified no significant within-group differences.

Paired t-tests using the paired concentrations for wet faeces identified: a significant fall in total SCFA concentration in the control group between baseline and end of radiotherapy (p=0.044), and a significant fall in butyrate concentration in the same group (p=0.030).

Using the wet paired values, a significant fall in valerate concentration was detected in the low fibre group (p=0.038) and a significant fall in iso-valerate concentration in the high fibre group (p=0.044) between baseline and end of radiotherapy.

4.5.4 Exploratory analysis: sample water content

Stool water content was measured by lyophilisation (freeze drying) of stool samples. An analysis of the change in percentage water content of the faecal samples was undertaken to examine whether significant within-group differences were apparent between baseline and the end of radiotherapy.

This identified that the percentage water content increased between baseline and the end of radiotherapy in the low fibre group (p=0.043). Percentage water content of samples obtained from the control and high fibre groups showed no significant differences between these time-points (**Table 4.13**).

Table 4.13 Difference in percentage water content of faecal samples

	Control n=16	Low fibre n=15	High fibre n=10
Mean (sd) % water content of sample after lyophilisation			
Baseline sample	73.8 (6.4)	74.2 (7.4)	75.9 (5.4)
End of RT sample	74.2 (6.0)	77.6 (6.9)	76.2 (6.6)
Paired t-test P value	0.864	**0.043***	0.872

Key: RT: radiotherapy, *significant: p<0.05

4.6 Quality of Life (IBDQ) scores

Scores obtained from patients' responses to the full 32-question IBDQ were used as the quality of life (QoL) measure for the trial. Scores at acute time-points and change in scores between time-points were examined for significant differences between groups.

All analyses using the IBDQ scores were treated as secondary trial outcomes. A one way ANOVA identified no differences between groups in scores at acute time-points (**Table 4.14**).

However, a significant difference in the change in IBDQ scores between baseline and end of radiotherapy was identified between groups (p=0.012).

Post-hoc, pair-wise, comparison between groups (Bonferroni method) identified this significant difference (p=0.010) was between the control and high fibre groups. The difference in the change in score of 17.2 points was in favour of the high fibre group.

Table 4.14 IBDQ scores and change in score

	Time-point	Control n=53	Low fibre n=52	High fibre n=54	*ANOVA p value*
IBDQ score: Mean (sd)					
IBDQ Baseline score	Start of RT	195.6 (17.5)	196.1 (23.8)	191.7 (26.0)	0.556
IBDQ Nadir score	Lowest on treatment	162.5 (33.1)	171.0 (28.2)	168.0 (32.0)	0.368
IBDQ End RT score	End of RT	171.7 (32.5)	178.8 (26.6)	185.0 (28.0)	0.065
IBDQ Change in score: Mean (sd)					
IBDQ Nadir change	Baseline to Nadir	-33.0 (31.7)	-25.0 (27.5)	-23.7 (33.2)	0.245
IBDQ End RT change	Baseline to end RT	-23.9 (32.0)	-17.2 (26.5)	-6.7 (30.2)	**0.012***

Key: Negative values represent a fall in score (worsening symptoms), RT: radiotherapy, *significant: $p<0.05$

Computation of IBDQ AUC values (indicative of symptom burden on QoL) for 153 patients (control: 53; low fibre: 50; high fibre: 50) resulted in a median (range) IBDQ-AUC for the cohort of 143 (48 - 592). Analysis of the difference between groups in acute IBDQ AUC identified no significant differences between groups ($p=0.600$) Kruskal Wallis' non-parametric test.

4.7 Discussion of clinical findings

The hypothesis for this trial was that a high fibre diet (18 – 22 g NSP / day) would reduce or prevent gastrointestinal symptoms in patients receiving radical pelvic radiotherapy. It was postulated that the mechanism of action of dietary fibre was via its fermentation product, SCFAs, which have anti-inflammatory properties and through its beneficial effect on stool frequency and form.

The results of the trial indicate that manipulating fibre intake does have a beneficial effect on gastrointestinal symptoms and thus the first part of the trial hypothesis can be accepted. However, the postulated mechanism of action of fibre needs further exploration and has not been unequivocally demonstrated by the trial's results.

The trial's primary endpoint was the difference in the change in score from baseline (start of radiotherapy) to nadir (worst) between groups with a difference of 6 points or more representing a clinically significant difference. The difference in score between groups between these points was not significant. However a significant difference was identified using the time-points baseline to end of radiotherapy.

Between baseline and end of radiotherapy, the high fibre group's IBDQ-B score fell -3.1 points compared to the control group, whose score fell -10.8 points, thus representing a clinically significant difference of -7.7 points and indicating a beneficial effect of high dietary fibre on gastrointestinal symptoms. However, no significant difference was identified between the change in IBDQ-B score between the low and high fibre groups. Further, the fall in score of the control group was -3.4 points more than that of the low fibre group indicating that low fibre advice is no better than no dietary advice.

The lack of a significant difference between the high and low fibre groups is puzzling. Firstly, the primary endpoint of the trial was the difference in IBDQ-B score between baseline and nadir and the difference between baseline and end of radiotherapy was a secondary endpoint. Could the study have been underpowered to detect a difference in this secondary endpoint resulting in a lack of difference between the high and low fibre groups? It is felt that under-powering of the study is unlikely. The nadir point was chosen to correspond to worst symptoms and thus the point of maximum possible difference between groups.

However, data used to power the study came from previous pelvic cohorts in which the mean (sd) change in IBDQ-B score between baseline and end of radiotherapy was equal to -9.3 (8) points, equating to a 15% change in score[24 46 75 76]. The Fibre study sought to find a clinically significant a 6 point (10%) difference in the change in score and had 90% power to detect a difference between any trial groups. It recruited the required 156 patients and actually included 159 patients with evaluable data in the analysis. Therefore, the difference that has been observed between the high fibre and control groups is not thought to be due to chance.

A further possibility that could have affected the results could have been that the trial groups were unbalanced at baseline and that the control group exhibited patient or treatment characteristics which negatively influenced the results. Treatment related factors which might have rendered the control group more susceptible than the low fibre group to new onset gastrointestinal symptoms include radiotherapy dose, fraction size, treatment time, tolerance to concomitant chemotherapy, previous surgery and history of inflammatory pathology in the bowel. Patient related factors which negatively influence outcomes include increasing age, low BMI[46], current smoking and use of anti-hypertensive medication and / or HMG CoA reductase inhibitors (statins)[50].

However, patients were stratified at randomisation by pelvic site and concomitant chemotherapy and the analysis of baseline characteristics identified that in terms of the main treatment-related parameters, trial groups were balanced. It is acknowledged that capture of additional information regarding previous surgery would be valuable as this can affect the movement of bowel structures, organ mobility and thus actual dose received. Further, data on precise dose, agent and tolerance to concomitant chemotherapy would certainly be valuable. Capture of details regarding previous surgery and chemotherapy administration would necessitate closer scrutiny of medical and pharmacy records, some of which are lodged in Trusts external to the Royal Marsden NHS Foundation Trust, which acts as the radiotherapy 'partner' to other host trusts administering chemotherapy agents and obviously retaining medical records. It is also recognised that not only do chemotherapy agents themselves cause gastrointestinal disturbance but additional medications which have known effects on gastrointestinal function may have influenced outcomes.

Patients were stratified for concomitant chemotherapy at randomisation and thus those in receipt of chemotherapy agents during radiotherapy were balanced between groups at the start of treatment. Chemotherapy agents received by patients in this study included the anti-metabolite, Capecitabine and alkylating or DNA cross-linking agents, Mitomycin C and Cisplatin (**Table 3.1**). Of these agents, oral Capecitabine, through its metabolite 5FU (fluorouracil) is the most likely to cause diarrhoea. However, capture of the incidence of diarrhoea due to chemotherapy *versus* that due

to radiation-induced damage would have been difficult. A detailed evaluation of patients in whom Capecitabine dose was reduced due to severity of new-onset diarrhoea would have been complicated by the current lack of standardisation in the capture of on-treatment toxicity (e.g. consistent use of CTCAE v.4) and the fact that such patients would probably have been advised to increase their use of the anti-diarrhoeal drug Loperamide thus complicating the analysis of true cause and effect.

In addition to anti-cancer agents, other GP-prescribed medications may have adverse effects on gastrointestinal function and similarly could have confounded toxicity outcomes. These drugs include: the anti-diabetic drug Metformin; anti-emetics such as Ondansetron, Metaclopromide and Domperidone; opiod analgesics (codeine phosphate) and antibiotics. Capture of precise details regarding duration of use and dose of these agents or indeed concomitant use of anti-hypertensive agents and statins (which conversely may have improved outcomes) is complicated by poor patient recall and lack of comprehensive, accessible details regarding non-hospital prescribed medications on NHS Trust-based electronic patient records or notes. Contact with patients' GP is the only reliable method of gathering such information and this can be very labour-intensive[50]. Capture of additional patient-related details such as smoking status could however have been usefully captured at randomisation.

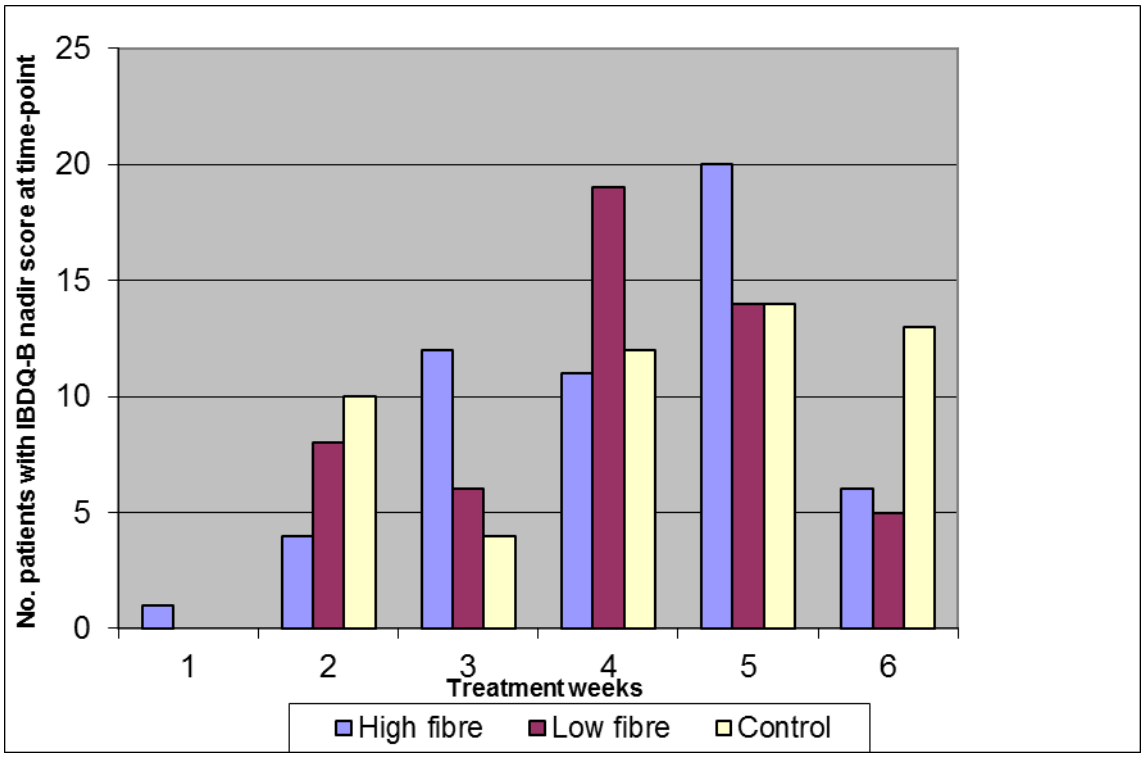
The lack of difference between the low and high fibre groups may be an artefact of the known difficulties in using symptom scoring tools as indicators of toxicity. We choose to use a tool (IBDQ-B) that we had previously validated in the acute radiotherapy setting and were confident that it was able to capture the subtle differences in symptoms that patients experience[6]. However, it is acknowledged that we did not use other tools which may have provided historical context (RTOG/EORTC) or use additional tools that would have provided more detailed information on incontinence for stool such as the Vaizey questionnaire[242], or urinary toxicity since it is not uncommon for patients to report both urinary and stool incontinence together. Use of multiple scoring tools is potentially burdensome for patients and thus in the fibre study, the number of questionnaires was kept to a minimum in view of the fairly intense nature of the dietary intervention.

However, the question remains as to how well symptom scoring tools reflect toxicity? In the low fibre group, other issues may have contributed to toxicity (e.g. urinary incontinence) that were not picked-up by the IBDQ-B and thus the change in score used as the primary outcome measure did not accurately reflect the true symptom burden. Some authors in the systematic review of fibre and IBD showed clear relationships between disease activity indices[208 216 241] and objective markers of gastrointestinal damage (e.g. endoscopy scores) however these endpoints are generally clinician completed items. When additional patient-reported items (e.g. symptom diaries) are requested, they fail to correlate with these more objective end-points[208]. Investigators in the radiotherapy setting have reported that nadir histological damage occurs prior to peak of worst symptoms[22]. Others investigating the onset of symptoms versus gastrointestinal damage in ulcerative colitis have noted a clear separation of two weeks between the emergence of microscopic or molecular damage to the gastrointestinal mucosa and onset of worst symptoms[199].

Since research in the radiotherapy setting rarely includes evidence of toxicity obtained in human tissues, the use of symptom scoring tools will continue and the choice of symptom scoring tool(s) may be challenged. Even with a validated tool other unforeseen problems in the research setting can emerge. One study in the systematic review of fibre manipulation during radiotherapy using a validated (prostate) scoring tool upon which the study was statistically powered was unable to identify significant differences between groups due to the choice of pelvic cohort (prostate cancer patients) who exhibited so few symptoms that significant differences between groups could not be identified[222].

It is curious that the high fibre group in the current study commenced treatment with the lowest mean IBDQ-B score (worst symptoms) and yet ended treatment with the highest score (least symptoms) whilst the control group, who started treatment with the least symptoms, ended treatment with the worst. A brief exploratory analysis of the distribution of nadir scores by study group (**Figure 4.5**) shows that more patients in the control group experienced nadir scores towards the end of treatment.

Figure 4.5 Number of patients with IBDQ-B nadir scores by treatment week



The reason for this is unclear but may have influenced the results by accentuating the difference between the high fibre and control groups at the end of radiotherapy. The possibility that patients in the control group had longer treatment times (i.e. more patients in this group remained on treatment in week 6) should not have influenced the distribution of nadir scores in this group. Groups were balanced for pelvic site at randomisation and treatment protocols are standard so each trial group will have contained a comparable number of patients on 6 week schedules.

The overall symptom burden, as indicated using the measure IBDQ-B AUC was not significantly different between groups. The effect of using the IBDQ-B AUC score should be to smooth differences between severe peak and moderate sustained toxicity in the single score. However, it is acknowledged that a fall in score in the IBDQ-B of 6 points may be due to a one-point change in score on six questions versus a six point change in score on one question. The relevance of this distinction in the acute and late setting requires further exploration. Our group and others have previously shown that moderate but sustained toxicity in the acute setting predicts more strongly for the emergence of late effects than a single severe spike of symptoms[46 47]. However, the importance of a small change in score in many questions versus a large change in score

in one or two questions would require a validation study with careful design to ascertain, in terms of toxicity, if these are equitable.

In summary, it is not immediately clear why the trial produced a significant result between the control and high fibre groups, in favour of the high fibre group but not between the high and low fibre groups. If fibre truly has a protective effect, a significant difference would have been expected between the low and high fibre groups. Is it possible that the measurement of fibre intake was flawed or that the planned differential in fibre intake between groups was not achieved in practice or that some other factor can account for this outcome? A more detailed analysis and discussion of nutritional findings (**Chapter 5**) may shed light on these questions.

The conducting of a randomised controlled trial was justified on the basis of a lack of robust evidence from previous studies regarding the efficacy of manipulating fibre intake in the radiotherapy setting. The hypothesis for the current study was that dietary fibre would prevent or reduce gastrointestinal symptoms arising during treatment. If a positive effect of fibre on the emergence or severity of symptoms (reflected in the IBDQ-B score) could be demonstrated, it was anticipated that this might be reflected in enhanced concentrations of faecal SCFA and if so a tentative conclusion could be reached that the reduction in symptoms was due (or partly due) to a reduction in inflammatory processes mediated by SCFA. It is acknowledged that these hypotheses are very tentative. However, no previous studies had explored the potential of fibre to influence toxicity via this mechanism and very little progress has been made on the identification of a suitable biomarker of toxicity in this setting.

Measurement of SCFA was utilised in three studies identified in the systematic review of fibre and IBD. Each examined the change in total SCFA and individual SCFA: acetate, butyrate and propionate after: 20 g/d of oat bran supplementation for 3 months in 19 patients with quiescent ulcerative colitis[241], 20 g/d of psyllium supplementation for 3 months in 7 patients with ulcerative colitis in remission[194] and 24 g/d of inulin supplementation for three weeks in 20 patients with pouchitis in remission[216]. All reported a significant increase in butyrate concentrations following supplementation but no significant changes in acetate or propionate or total SCFA. All used gas

chromatography (GC) techniques for SCFA measurement although only one study specified their results as concentrations in wet or dry faeces[216].

Since, it is feasible to measure the concentration of all fatty acids in one GC run, all individual acids and total SCFA were measured in the current study and the results reported as both wet and dry values. Forty one paired samples were obtained. No significant differences were identified (using wet or dry weights) in the change in concentrations, between groups. However, significantly reduced concentrations of butyrate and total SCFA were identified in the control group between start and end of radiotherapy using wet faeces. Further, it was noticed that the water content of faecal samples from the low fibre group was significantly increased to 77.6% (±6.9) at the end of radiotherapy indicative of loose and unformed stool[243].

The change in Butyrate and total SCFA observed in the fibre study is intriguing. However, measuring SCFA in faeces is not straightforward and is the result of dynamic process of both production and absorption, and therefore faecal SCFA is not just a marker of SCFA production alone. SCFA absorption is impacted by colonic gut transit time, which itself may be altered in those with GI toxicity and those with different fibre intakes. Therefore faecal SCFA concentrations reflect production (affected by fibre intake) as well as absorption (affected by toxicity and fibre intake).

A decrease in faecal SCFA might be expected if pelvic radiotherapy resulted in a reduction in the total number of bacteria. There is limited evidence that this occurs. One older pre-clinical study using outdated culture-dependent techniques reported reduced Lactobacilli and Bifidobacteria following irradiation[117]. A small pilot study using more modern techniques reported a modified bacterial profile following pelvic radiotherapy[48] and a further small pilot reported a reduction in Lactobacilli and Bifidobacteria following pelvic radiotherapy in placebo and prebiotic supplemented groups[223]. Increased gut transit time (GTT) with reduced colonic fermentation time would also be expected to reduce concentrations of SCFA and there is evidence that this occurs[244 245].

A high fibre intake might be expected to increase SCFA concentration. Although increasing SCFA concentration does not necessarily reflect increased production[246]. In the current study, reduced bacterial numbers combined with increased GTT may have had differing effects on SCFA concentrations. However, further investigation is warranted in adequately powered samples. Powering of future studies will need to take account of the widely varying levels of these acids with 10-fold differences in the concentrations of faecal SCFA having been reported between individuals[156].

A further physiological measure (stool output or frequency and form) was included in the fibre study to provide additional insight into gastrointestinal toxicity and evidence (if this existed) of the therapeutic efficacy of fibre during radiotherapy. It is acknowledged that there is no recognised method of capture or synthesis of daily stool chart data. The Bristol Stool form scale provides a useful and readily interpretable measure of stool consistency but it must be used in conjunction with other measures such as stool frequency to reflect changes in bowel function during treatment. Whilst many patients are willing to complete stool diaries or charts, synthesis of patient-reported data is extremely time-consuming. The current study used daily patient-completed data and four different measurements to help reflect the change in bowel habit during treatment. These methods are not validated. It is hoped that as an aside to this study, a correlational analysis be conducted of patient-reported stool data with change in scores in specific IBDQ-B questions. This might enable a more precise definition of a diarrhoea day and abridgement of the data collected at present. Machine-readable stool charts would represent a considerable improvement on the manual methods of data extraction currently employed.

Stool data produced in the fibre study yielded some interesting results. Stool frequency and form was not significantly different between groups at the start, mid-point or end of radiotherapy and incidence of loose or unformed stool was comparative between groups. These findings are positive in the sense that they challenge the current advice to restrict fibre in the clinical setting but fall short of identifying a specific physiological effect of increased dietary fibre. However, one very important finding emerging from the analysis of stool chart data in the current study was the marked increase in the use of anti-diarrhoeal medication by the high fibre

group towards the end of treatment. What effect this had on IBDQ-B scores is impossible to discern. However, it is possible that it masked symptoms and affected symptom scores in the high fibre group at the end of treatment. Patients are free to use over-the-counter preparations and encouraged to use loperamide as first line treatment if they are experiencing difficulty with loose or unformed stool. Part of the reason for this is to ensure continuity of radiotherapy treatment. However, anti-diarrhoeal medication may be taken for prophylactic or therapeutic use and in the current study patients were not asked to define this, although it is perhaps one simple improvement that could be readily introduced in future research.

Quality of Life is an increasingly important clinical outcome in all research and more especially in the current era of increased cancer survivorship. Quality of life outcomes in patients undergoing pelvic radiotherapy have been explored in three previous studies including one of those included in the systematic review of the efficacy of fibre in patients undergoing pelvic radiotherapy[222 247 248]. The most recent of these by Pettersson (n=112 prostate cancer patients with evaluable data at the end of radiotherapy) used the quality of life measure EORTC QLQ-C30 (v.3) to evaluate the effect of gastrointestinal symptoms on quality of life. The EORTC QLQ-C30 (v.3) is a 30-item oncology specific questionnaire, containing six functional scales (physical, emotional, cognitive, social, role, global health), three symptom scales (fatigue, pain, nausea or vomiting) and six single items assessing symptoms and the financial impact of disease. No significant differences in health related quality of life outcomes were found between those randomised to standard care and those following a low insoluble fibre, low lactose diet.

In the three-arm study by Ravasco[248], colorectal patients (n=111) were randomised at the start of radiotherapy to receive: individualised dietary counselling, protein supplements or normal ad libitum diet. Quality of life was measured using the same 30-item EORTC QLQ-C30. The results of this study have direct relevance to the findings of the fibre study. The study demonstrated that manipulating the whole diet based on regular foods, rather than supplementing isolated components of the diet (e.g. protein), was much more effective in maintaining significantly improved nutritional status and quality of life during radiotherapy compared to supplementation or ad

libitum intake. Further, efficacy of the benefit of individualised dietary advice persisted for 3 months after radiotherapy treatment and in a recent long-term follow-up analysis (median 6.5 years) was associated with reduced toxicity ($p<0.001$) and improved QoL ($p<0.002$)[249].

The study by Isenring in a mixed cohort of head and neck and gastrointestinal cancer patients using the medical Nutrition Therapy (Cancer/Radiation Oncology) protocol of the Amercan Dietetic Association (now the Academy of Nutrition and Dietetics) using the same QoL measure also reported improved global QoL ($p=0.009$), weight maintenance and nutritional status compared to those receiving usual care[247 250]. Higher protein intake ($p<0.001$), total energy intake ($p=0.029$) and a trend towards increased dietary fibre intake was also reported in the group receiving nutritional counselling versus usual care[250].

In the light of these observations, it is considered a limitation of the Fibre study that it did not employ an oncology-specific Quality of Life tool. Whilst the IBDQ scores are easily captured in a study focussing on the IBDQ-B, use of the EORTC QLQ-C30 would have allowed comparison with these previous studies. However, in line with the findings of these studies, the fibre study has identified a significant difference between groups in the change in IBDQ score between the start and end of radiotherapy in favour of the high fibre group whose score fell just -6.7 points compared to the control group whose score fell -23.9 points, a difference of -17.2 points.

In summary, in the group instructed to follow a high fibre intake during radiotherapy a beneficial effect was observed on gastrointestinal symptoms and quality of Life using a non-oncology scoring tool. Thus, the first part of the trial (research) hypothesis could be accepted. However, many questions remain. What was the daily intake of fibre intake in this group and how did this compare to other study groups? How was the intake of fibre assessed? What was the difference in fibre intake between study groups? Would this difference have been sufficient to cause a differing effect on gastrointestinal symptoms between groups?

These questions are addressed in the next chapter which also assesses whether the study intervention has had a negative impact on nutritional status including body weight and BMI. Increased intake of dietary fibre has been associated with early satiety and energy intake and thus the impact of the trial interventional diet on micronutrient intake and palatability of diet are also explored.

CHAPTER 5

A randomised controlled trial to investigate the role of low or high fibre diets in patients undergoing pelvic radiotherapy: Nutritional Findings

5.1 Introduction

This chapter presents the nutritional results of the randomised controlled trial. An assessment of the validity of these findings is crucial to ascertaining whether the results presented in **Chapter 4** can be attributed to the intervention. This requires assessing whether patients were able to comply with their target fibre prescription, what intakes they actually achieved in practice and whether a sufficient differential in fibre intake occurred between groups. Non-compliance might explain why the trial failed to identify a difference in gastrointestinal symptom scores between the high and low fibre groups.

Few of the studies in the systematic review of fibre manipulation in IBD patients measured background diet. Further, in the studies identified in the review which did use a dietary intervention, few measured compliance or stated the criteria for assessing compliance. Advice regarding achievement of compliance with intervention target in the fibre study was given by a registered dietitian and the interventional tools (the Guidance booklet and fibre exchange diaries) were designed specifically to help patients meet their fibre target. The guidance booklet contained information on portion sizes but did not include photographic material helping patients to estimate their portion sizes.

Analysis of fibre intake is a complex process, not least because of the differing definitions of fibre in use. The gold standard for the capture of dietary fibre intake data is seven days which takes account of daily fluctuations. However, extraction of data from 7 day food diaries is labour intensive and if the data is entered into a dietary software package there are many steps in the data entry process where errors can be made.

The average time for capture of data from seven days food diaries is three hours. Thus the fibre study employed two researchers blinded to trial interventional group to extract food intake data and enter this into dietplan software. Efforts were made to ensure standardisation between these two researchers including provision of appropriate training and standardisation in methods employed.

The objectives of this chapter are as follows:

1. To investigate the degree of variation between investigators in the capture of dietary intake data from seven day food diaries.

2. To measure fibre intake in the recruited patients at week one and final week of radiotherapy.

3. To measure compliance with fibre intervention using pre-determined cut-offs of fibre intake for patients in the intervention groups.

4. To measure the effect of the intervention on anthropometric variables: body weight and BMI.

5. To measure the effect of the intervention on macronutrient intake given the finding that energy and protein intakes are associated with improved quality of life outcomes.

6. To measure the effect of the intervention on micronutrient status given the perception that high fibre intake leads to early satiety and compromised energy intake.

7. To measure the acceptability and palatability of the intervention so that in the event that the intervention is deemed appropriate to be more widely adopted, then the diet itself and the interventional tools are deemed to be acceptable by patients.

5.2 Trial results: presentation

The following conventions are used in the presentation of results. Negative values for a change in fibre, nutrient intake, body weight and BMI between time-points indicate a fall compared to baseline.

For statistical analyses, where one way ANOVA has been performed, the data has been assessed for normality and found to be acceptable to consider as normally distributed. Non-normally distributed data are analysed using an appropriate non-parametric test.

All nutritional endpoints are secondary and any statistically significant findings should be viewed with caution as the trial was not powered to detect differences in these endpoints.

5.3 Evaluable data

The completeness of nutritional end-points is shown in **Table 5.1**.

Table 5.1 Evaluable nutritional data (total n=159)

Time point	Control n=53	Low fibre n=52	High fibre n=54	% Return* All groups
Weight (kg)				
Baseline (start of radiotherapy)	53	52	54	100
End of radiotherapy	53	52	54	100
BMI (kg/m^2)				
Baseline (start of radiotherapy)	53	52	54	100
End of radiotherapy	53	52	54	100
7 Day Food Diaries				
Baseline (start of radiotherapy)	51	47	48	92
End of radiotherapy	44	41	43	81
Number of paired diaries returned	44	41	42	127
Fibre Exchange Diaries				
Completed diaries returned	NA	34	36	66
Ease of Use of Fibre in Foods booklet questionnaire				
Number completed	NA	22	22	NA
Weekly 24 Hour Recalls				
Number completed in total	102	107	103	312
Average number completed per group	1.9	2.1	1.9	2.0
Visual Analogue Scales (palatability of trial diet)				
Number completed	NA	40	38	74

Key: * Percentage calculated on basis of n=159 (all groups) or n=106 (low & fibre groups).

It is important to note that the 7 day food diaries obtained for week one of radiotherapy were completed by patients after randomisation and thus recorded dietary intake data after dietetic advice.

Of the nutritional outcomes, eight patients had missing weight data on body weight at the end of radiotherapy and therefore weight scores were carried forward from the start of treatment.

Patients in all trial groups were asked to complete 7 Day Food Diaries for the first and last week of radiotherapy. Of the expected 318 diaries given to patients, a total of 274 were returned. Of these, 127 were paired diaries for week one (i.e. after receipt of dietary advice for interventional groups) and the last week of radiotherapy.

An average of two 24-hour dietary recalls were conducted per patient (all groups) whilst on treatment. Patients in the low and high fibre groups (n=106) were additionally requested to keep a fibre exchange diary detailing daily self-estimated fibre intake. Of these, 66% returned fibre exchange diaries at the end of radiotherapy.

Forty four patients (low fibre: 22; high fibre: 22) voluntarily completed an Ease of Use questionnaire with reference to the Fibre in Foods booklet at the end of radiotherapy. This activity was undertaken in response to a request from a patient representative on the Fibre Trial Steering Committee.

5.4 Between researcher analyses: dietary intake data

The input of dietary data is laborious, time intensive and therefore expensive. For large samples with many completed 7 day food diaries, it often necessitates more than one researcher to undertake data entry.

In the current study, two researchers (R1, R2) extracted details of dietary intake from the patient-completed 7 day food diaries. R1 (a research nurse trained in the use of Dietplan software) analysed 100 diaries and R2 (a registered dietitian with extensive experience of the Dietplan software) analysed 147 diaries. However, dual dietary data entry is notoriously problematic, with potential for wide variation in interpretation of food diaries and therefore poor reliability.

In order to measure the accuracy of data entry, the effect of different researchers on estimates of energy and fibre intake were compared to that of the current author (LW) as the gold standard.

Briefly, a sample of end of radiotherapy food diaries selected at random using a random number generator by the data manager were used for this analysis (control: 6, low fibre: 6, high fibre: 6). All researchers were blinded to the patient's group allocation.

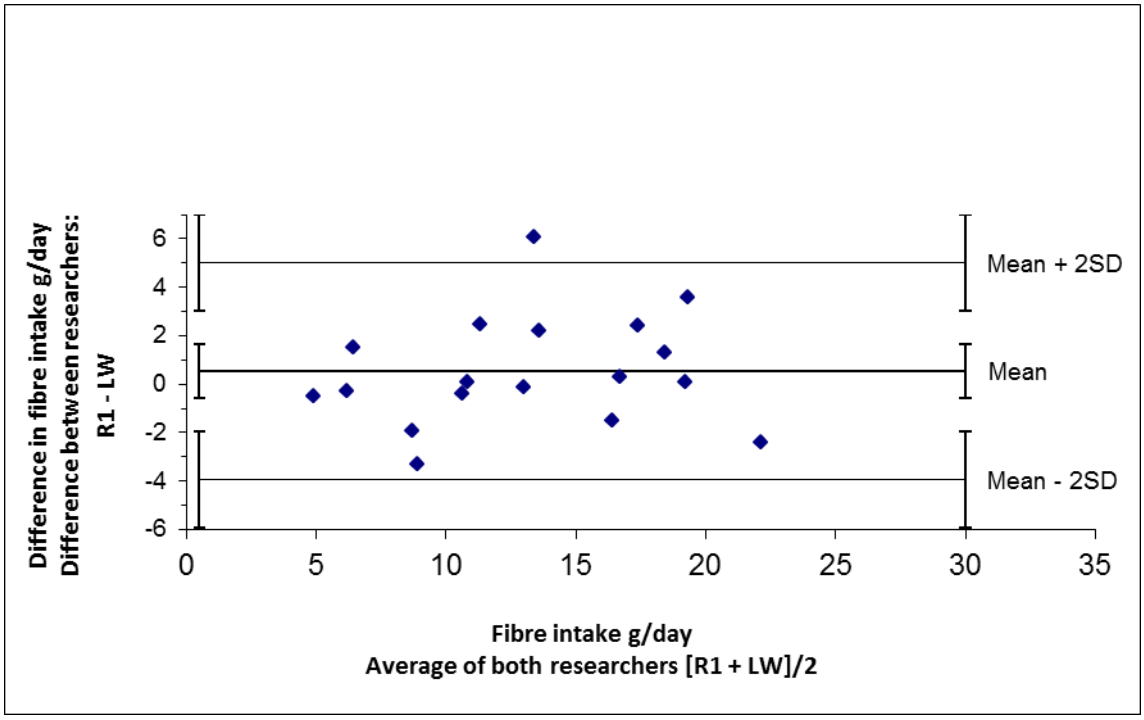
ANOVA identified no significant differences between researchers in the estimated energy (kcal/day) or fibre intake (g NSP/day) for the six diaries from each study group (**Table 5.2**).

Table 5.2 Estimation of fibre and energy intake: between researcher analysis

Trial Group, n=6 diaries / group	Mean (sd) fibre intake g NSP/day			***ANOVA p value***
	R1	**R2**	**LW**	
Control	11.3 (5.3)	10.7 (4.3)	10.6 (4.2)	0.965
Low fibre	10.2 (3.7)	8.9 (1.7)	9.5 (1.9)	0.695
High fibre	18.8 (2.2)	18.8 (3.7)	18.5 (2.5)	0.988
Trial Group n=6 Diaries / group	Mean (sd) estimated energy intake kcal /day			***ANOVA p value***
	R1	**R2**	**LW**	
Control	1873 (573)	1689 (391)	1819 (391)	0.778
Low fibre	1569 (453)	1395 (377)	1402 (342)	0.694
High fibre	2294 (296)	2105 (407)	2148 (213)	0.567

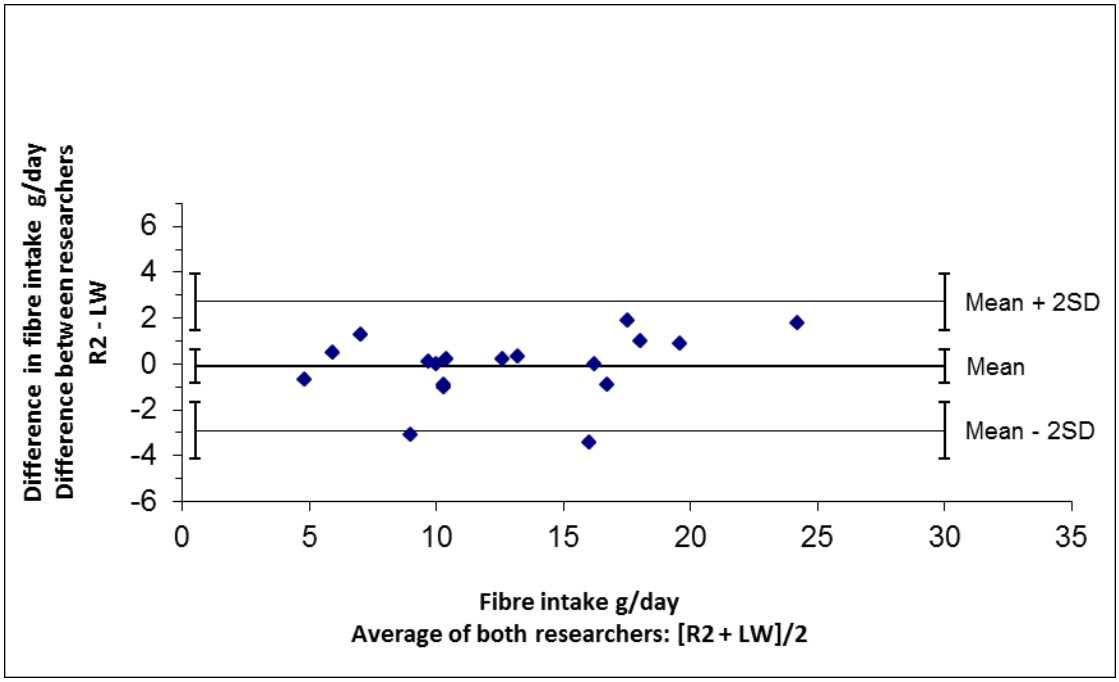
Bland Altman plots were used to examine the level of agreement between each researcher versus LW in the estimation of fibre intake (**Figures 5.1** and **5.2**).

Figure 5.1 Bland-Altman plot of dietary fibre intake for 18 food diaries analysed by Researcher 1 (R1) *versus* gold standard (LW)



Summary data: Mean 0.5, CI 1.68 to -0.60

Figure 5.2 Bland-Altman plot of dietary fibre intake for 18 food diaries analysed by Researcher 2 (R2) *versus* gold standard (LW)



Summary data: Mean -0.1, CI 0.61 to -0.81

The mean difference between R1 and LW in the estimation of daily fibre intake was 0.5 g NSP/day (n=18 diaries). The mean difference between R2 and LW in the estimation of daily fibre intake was -0.1 g NSP/day (n=18 diaries).

As this analysis shows, better agreement was achieved between the two dietitians (R2 and LW) than between the research nurse and dietitian (R1 versus LW). However, importantly, mean differences between R1 and LW and between R2 and LW were low and there was no systematic trend for the level of agreement or disagreement depending upon actual fibre intake (i.e. differences were evenly distributed across low, medium and high intakes of fibre).

Level of agreement between investigators was judged to be sufficiently good to have confidence in the estimation of further dietary intake data from the 7-day food diaries and that further nutritional analysis using this data was not subject to investigator bias.

5.5 Analysis of dietary fibre intake

Dietary fibre intake was assessed for each patient from 7 day food diaries completed during week one and the final week of radiotherapy. Fibre intake for week one of radiotherapy thus reflects intake following randomisation.

Food diaries detailing dietary intake for week one of radiotherapy were returned from 146 patients and for the final week from 125 patients. Mean (sd) intakes of dietary fibre for week one and final week of treatment (three methods for comparison) by trial group are shown in **Table 5.3**

One way ANOVA was used to compare the difference in the group mean daily fibre intake across trial groups for both weeks. A significant difference in intake (all methods) was identified between groups at both the week one and final week time-points (**Table 5.3**).

Table 5.3 Intake of dietary fibre: week one and final week of radiotherapy

Fibre intake reporting method	Control	Low fibre	High fibre	ANOVA p value
	Mean (SD)	Mean (SD)	Mean (SD)	
	n=51	n=47	n=48	
Mean (sd) daily fibre intake during week one				
Fibre: NSP g /day	13.6 (5.3)	10.2 (3.4)	17.1 (4.8)	<0.001
Fibre: NSP g / 1000 kcal day	7.5 (2.0)	6.4 (2.3)	9.2 (2.2)	<0.001
Fibre: AOAC g/day	17.6 (6.9)	13.4 (6.7)	21.7 (5.6)	<0.001
Fibre: AOAC/1000 kcal day	9.6 (2.5)	8.3 (3.2)	11.7 (2.7)	<0.001
Mean (sd) daily fibre intake during final week				
	n=44	n=41	n=43	
Fibre: NSP g /day	12.2 (5.2)	8.9 (2.9)	15.7 (5.1)	<0.001
Fibre: NSP g / 1000 kcal day	7.2 (2.6)	5.8 (2.1)	8.7 (2.3)	<0.001
Fibre: AOAC g/day	15.7 (6.8)	11.6 (5.1)	19.8 (6.3)	<0.001
Fibre: AOAC/1000 kcal day	9.2 (3.5)	7.6 (2.5)	10.9 (3.0)	<0.001

Key: NSP: non-starch polysaccharide, AOAC: Association of Official Analytical Chemists, *statistically significant (P<0.05),

Post-hoc analysis (Bonferroni method) identified that during week one (i.e. after randomisation and following advice from the study dietitian regarding achievement of fibre target for interventional groups) the low fibre group consumed a mean -3.3 g NSP / day (95% CI: -1.1 – -5.6) less than the control group (p=0.001) and the high fibre group consumed a mean 3.6 g NSP / day (95% CI: 1.3 – 5.8) more than the control group (p=0.001). The difference in the mean fibre intake between the high and low fibre groups during week one was 6.9 g NSP / day (95% CI: 4.6 – 9.2).

During the final week of treatment, the low fibre group consumed a mean -3.3 g NSP / day (95% CI: -0.9 – -5.7) less than the control group (p=0.003) and the high fibre group consumed a mean 3.5 g NSP / day (95% CI: 1.1 - 5.9) more than the control group. The difference in the mean fibre intake between the high and low fibre groups during the final week of radiotherapy was 6.8 g NSP / day (95% CI: 4.4 – 9.2).

Within group analysis (paired t-test) using 127 paired diaries (control: 44, low: 41, high: 42) identified a significant fall in fibre intake in all groups between week one and the final week of radiotherapy ($p<0.05$ all comparisons).

5.6 Analysis of compliance

Analysis of compliance with fibre target identified that during week one, 77% of patients in the low fibre group were at least 80% compliant with fibre target (≤ 10g NSP / day). In the high fibre group, 79% of patients were at least 80% compliant with fibre target (≥ 18g NSP / day). However, in the final week of radiotherapy, 80% compliance was achieved by 83% of patients in the low fibre group but only 63% in the high fibre group.

Table 5.4 Compliance with target fibre intake

Time-point Compliance level	**Low fibre** n (%)	**High fibre** n (%)
Week one		
Compliance	n=47	n=48
80%	36 (77)	38 (79)
85%	34 (72)	34 (71)
90%	33 (70)	32 (67)
100%	27 (57)	20 (42)
Final week		
Compliance	n=41	n=43
80%	34 (83)	27 (63)
85%	34 (83)	25 (58)
90%	30 (73)	23 (54)
100%	25 (61)	16 (37)

Few patients achieved 100% compliance with fibre target. Although it appears that patients in the low fibre group, 27/47 (57%) of whom were 100% compliant at week one and 25/41 (61%) of whom were compliant in the final week of treatment may have found it easier to meet the target. In contrast, in the high fibre group, only 20/48 (42%) were 100% compliant at week one and 16/43 (37%) 100% compliant in the final week of treatment.

This may partly be explained by impaired overall food intake. Reduced total energy intake at the end of radiotherapy may have favoured compliance with target in the low fibre group (as they may have been reducing overall food intake, as opposed to fibre

intake specifically). However, this would have had the opposite effect in the high fibre group. The quantity of fibre intake per 1000 kcal decreased by less than 1.0 g NSP / 1000 kcal in all trial groups between week one and final week (**Table 5.3**) suggesting little change in fibre intake over time and suggesting that it was not influenced by total energy intake.

A comparison of the proportion of the diet provided by carbohydrates for the low fibre group showed little change at week one (44% of total energy provided by carbohydrates) versus final week (45% from carbohydrates). These figures were comparable to the control (45% and 46%) and high fibre groups (46% and 45%) for the proportion of total energy from carbohydrates for both weeks respectively.

5.7 Total energy and macronutrient intake

Total daily energy intake (kcal/day) and intake of macronutrients (g/day) at week one and during the final week of radiotherapy was examined for differences between groups.

A reduction in total energy intake was seen in all groups between week one and the final week of radiotherapy amounting to mean reduction of 118 kcal in the control group, 122 kcal in the low fibre and 62 kcal in the high fibre group (**Table 5.5**).

One way ANOVA identified a significant difference in protein intake between groups in the final week of radiotherapy ($p=0.012$). Post hoc analysis identified this difference to be between the low and high fibre groups with a significantly reduced intake of protein in the low fibre group compared to the high fibre group of 14.6 g/day (95% CI for the difference: 2.7 – 26.5).

Table 5.5 Intake of macronutrients: week one and final week of radiotherapy

Nutrient	Control	Low fibre	High fibre	ANOVA p value
	Mean (SD)	Mean (SD)	Mean (SD)	
	n=51	n=47	n=48	
Mean (sd) intake at week one				
Total energy kcal / day	1833 (561)	1693 (415)	1898 (524)	0.134
Protein g / day	73.4 (21.6)	70.9 (16.7)	78.3 (20.6)	0.187
Fat g / day	71.1 (27.0)	69.7 (25.0)	75.6 (26.7)	0.511
Carbohydrate g / day	207.3 (71.6)	186.3 (47.4)	216.9 (62.9)	0.051
Mean (sd) intake at final week				
	n=44	n=41	n=43	
Total energy kcal / day	1715 (569)	1571 (496)	1836 (453)	0.062
Protein g / day	68.6 (24.5)	63.8 (19.8)	78.4 (22.7)	**0.012***
Fat g / day	65.9 (24.5)	63.2 (22.8)	73.0 (23.2)	0.144
Carbohydrate g / day	197.2 (72.8)	178.5 (66.1)	207.2 (57.7)	0.134

Key: *statistically significant (P<0.0125)

Total energy intake was reduced in all groups during the final week of radiotherapy although the difference between groups at this time-point was not significant (p=0.062).

Within group differences in total daily energy and macronutrient intakes between weeks one and the final week of radiotherapy were explored using paired t-tests for patients with diaries at both time-points (**Table 5.6**).

This analysis showed that, in the control group, total energy and protein intake fell significantly (p=0.010 and p=0.006 respectively) between week one and the final week of radiotherapy. Total protein intake also fell significantly (p=0.002) in the low fibre group.

Table 5.6 Total energy and macronutrient intake: within group analysis

Nutrient Time-point	Control		Low fibre		High fibre	
	Mean (sd)	Paired t-test	Mean (sd)	Paired t-test	Mean (sd)	Paired t-test
	n=44		n=41		n=42	
Energy kcal / day Week one	1886 (553)	**0.010***	1717 (425)	0.019	1944 (540)	0.132
Energy kcal / day Final week	1715 (569)		1571 (496)		1834 (458)	
Protein g / day Week one	76.0 (21.6)	**0.006***	72.2 (17.2)	**0.002***	80.2 (21.4)	0.497
Protein g / day Final week	68.6 (24.5)		63.8 (19.8)		78.3 (23.0)	
Fat g / day Week one	74.2 (27.5)	0.016	71.4 (25.6)	0.014	77.7 (27.6)	0.249
Fat g / day Final week	65.9 (24.5)		63.2 (22.8)		73.3 (23.4)	
CHO g / day Week one	210.6 (71.9)	0.073	186.0 (49.0)	0.345	221.0 (65.4)	0.084
CHO g / day Final week	197.2 (72.8)		178.5 (3.80)		206.0 (57.9)	

Key: CHO: carbohydrate, *statistically significant (P<0.0125 pairwise comparison)

Whilst the difference in total energy intake was not significantly different between groups at the end of radiotherapy, the fall in total energy intake using paired values (**Table 5.6**) in the high fibre group during the final week of radiotherapy (-110 kcal) was less than that in the control group (-146 kcal) and less than that in the low fibre group (-122 kcal).

It is possible that an effort to achieve the high fibre target may have positively influenced total energy intake although this cannot be verified. This finding is in contrast to the commonly held view that increasing fibre intake reduces appetite and energy intake. As this study and others have shown, in other healthcare settings[251], recommending a high fibre diet to patients receiving pelvic radiotherapy did not result in a lowering of total energy or macronutrient intake. A recent systematic review showed that of 44 studies investigating the effect of acute fibre treatments on appetite and energy intake, 61% of treatments did not enhance satiety and 78% did not reduce food intake[252].

5.8 Micronutrient intake

The effect of the intervention during radiotherapy on micronutrient intake was explored. One way ANOVA was used to compare differences between groups in vitamin and mineral intake during week one (**Table 5.7**) and the final week of radiotherapy (**Table 5.8**).

During week one, significant differences between groups are identified for the intake of minerals magnesium, iron and manganese. During the final week of radiotherapy, significant differences were identified between groups in the intake of vitamin K, magnesium, phosphorous, potassium, zinc and manganese ($p<0.0125$ for multiple comparisons at both time-points).

These results are exploratory as the study was not powered to examine these endpoints. Post-hoc analysis was not conducted. However, although not statistically significant, in all cases where significant between group differences have been identified, intake of micro-nutrients in the high fibre group is higher compared to the control and low fibre groups indicating a possible benefit of increased overall total energy intake.

Intakes less than the Reference Nutrient Intake (RNI) for adults over 50 years, using the minimum of the values given for males and females are also highlighted at both time-points (**Tables 5.7** and **5.8**). The RNI represents the value two sd above the Estimated Average Requirement (EAR) and the value at which the requirements for 97.5% of the population are being met.

During week one, the mean intakes of the various groups for vitamin D, potassium and selenium are below the RNI for all groups and in the final week of radiotherapy, intake of vitamin A, vitamin D, potassium, selenium and iodine was below the RNI.

Table 5.7 Micronutrient intake: week one of radiotherapy

Nutrient	Control	Low fibre	High fibre	ANOVA p value
	Mean (SD)	Mean (SD)	Mean (SD)	
	n=51	n=47	n=48	
Mean (sd) intake at week one				
Vitamin A µg retinol/d	605 (1156)	426 (311)**	789 (1927)	0.405
Vitamin B1 Thiamin mg/d	1.6 (0.7)	1.4 (0.4)	1.7 (0.6)	0.048
Vitamin B2 Riboflavin mg/d	1.7 (0.7)	1.6 (0.6)	1.7 (0.7)	0.624
Vitamin B3 Niacin mg/d	21 (7)	18 (6)	21 (7)	0.054
Vitamin B_6 mg/day	2.1 (0.7)	1.8 (0.5)	2.0 (0.7)	0.027
Vitamin B_{12} µg/day	5.5 (4.9)	4.3 (1.6)	5.9 (6.7)	0.277
Folate µg/day	270 (96)	236 (70)	279 (99)	0.045
Vitamin C mg/d	102 (56)	88 (51)	108 (62)	0.202
Vitamin D µg/d	3.2 (2.2)**	3.6 (3.4)**	4.0 (5.1)**	0.515
Vitamin E md/d	8.1 (3.8)	7.1 (3.0)	8.7 (4.6)	0.132
PUFA: n-3 g/d	0.5 (0.2)	0.5 (0.4)	0.6 (0.6)	0.161
PUFA: n-6 g/d	3.5 (1.7)	3.2 (2.2)	4.2 (3.0)	0.096
Vitamin K µg/d	67 (83)	52 (73)	74 (119)	0.518
Calcium mg/d	872 (295)	892 (380)	827 (312)	0.613
Magnesium mg/d	289 (108)	239 (55)**	305 (89)	**0.001***
Phosphorus mg/d	1252 (403)	1172 (282)	1319 (349)	0.125
Sodium mg/d	2709 (1291)	2367 (738)	2801 (1094)	0.119
Potassium mg/d	3210 (1242)**	2719 (685)**	3221 (827)**	0.015
Chloride mg/d	3895 (1594)	3474 (1008)	4075 (1601)	0.115
Iron mg/day	12.3 (5.5)	10.2 (3.0)	13.6 (5.9)	**0.004***
Zinc mg/d	8.8 (2.9)	8.7 (3.1)	10.0 (3.6)	0.100
Copper mg/day	1.4 (1.2)	1.0 (0.4)**	1.6 (1.2)	0.015
Selenium µg/d	39 (15)**	39 (12)**	43 (19)**	0.360
Manganese mg/day	3.5 (1.4)	2.9 (0.8)	3.8 (1.4)	**0.003***
Iodine µg/d	144 (81)	137 (74)**	121 (47)**	0.251

Key: *statistically significant (p<0.0125), ** Mean values for the group falls below the RNI Adults (UK)

Table 5.8 Micronutrient intake: final week of radiotherapy

Nutrient	Control	Low fibre	High fibre	ANOVA p value
	Mean (SD)	Mean (SD)	Mean (SD)	
	n=44	n=41	n=43	
Mean (sd) intake at week one				
Vitamin A µg retinol/d	418 (292)**	381 (253)**	551 (915)**	0.365
Vitamin B1 Thiamin mg/d	1.4 (0.5)	1.3 (0.5)	1.6 (0.6)	0.117
Vitamin B2 Riboflavin mg/d	1.6 (0.7)	1.5 (0.6)	1.6 (0.7)	0.645
Vitamin B3 Niacin mg/d	18 (7)	17 (7)	20 (8)	0.184
Vitamin B_6 mg/day	1.8 (0.7)	1.7 (0.7)	2.0 (0.8)	0.156
Vitamin B_{12} µg/day	4.6 (3.1)	3.9 (1.9)	6.1 (6.0)	0.057
Folate µg/day	255 (95)	227 (108)	255 (85)	0.308
Vitamin C mg/d	106 (66)	84 (60)	98 (57)	0.261
Vitamin D µg/d	2.8 (2.0)**	3.3 (3.3)**	3.4 (3.1)**	0.562
Vitamin E md/d	7.3 (3.8)	6.2 (2.6)	7.9 (3.9)	0.102
PUFA: n-3 g/d	0.4 (0.3)	0.5 (0.4)	0.5 (0.3)	0.690
PUFA: n-6 g/d	2.9 (1.5)	2.7 (1.8)	3.5 (2.8)	0.166
Vitamin K µg/d	57 (58)	35 (37)	81 (95)	**0.011***
Calcium mg/d	817 (321)	718 (304)	791 (256)	0.283
Magnesium mg/d	268 (114)**	203 (66)**	280 (83)	**0.000***
Phosphorus mg/d	1174 (431)	1011 (308)	1275 (343)	**0.005***
Sodium mg/d	2417 (1146)	2223 (837)	2796 (930)	0.027
Potassium mg/d	2928 (1251)**	2321 (819)**	3029 (903)**	**0.003***
Chloride mg/d	3556 (1637)	3191 (1090)	4054 (1337)	0.018
Iron mg/day	11.5 (5.4)	9.6 (3.9)	12.6 (4.5)	0.017
Zinc mg/d	8.5 (3.0)	7.3 (2.5)	9.4 (3.1)	**0.005***
Copper mg/day	1.2 (0.8)	1.0 (0.3)**	1.3 (0.7)	0.016
Selenium µg/d	37 (16)**	35 (12)**	40 (19)**	0.410
Manganese mg/day	3.2 (1.4)	2.5 (1.0)	3.6 (1.7)	**0.002***
Iodine µg/d	139 (84)**	122 (55)**	121 (52)**	0.365

Key: *statistically significant ($p<0.0125$), ** Mean values for the group falls below the RNI Adults (UK)

5.9 Weight and BMI

No significant differences were identified in body weight between groups at the start or end of radiotherapy or in the change in body weight between these time-points (**Table 5.9**).

Weight fell in all groups during treatment. The wide standard deviation of weight change in the low fibre group shows that there was considerable individual variation in weight change in this group.

However, a comparison of the change in body weight within groups (paired t-test) revealed no significant within group differences in the pair-wise comparisons.

Table 5.9 Body weight and change in weight

Time-point	Control	Low fibre	High fibre	*ANOVA p value*
Weight (kg): Mean (sd)				
n	53	52	54	
Start of Radiotherapy	81.0 (18.5)	78.3 (18.1)	77.5 (15.6)	0.559
End of Radiotherapy	80.4 (18.3)	77.5 (17.6)	77.0 (16.3)	0.543
Weight change (kg): Mean (sd)				
n	53	52	54	
Weight change Start to end RT	-0.6 (2.1)	-0.8 (4.9)	-0.5 (2.1)	0.814

Key: sd: standard deviation, RT: radiotherapy *significant: $p<0.05$

Further, no significant differences in mean BMI between trial groups at the start or end of radiotherapy or the change in BMI between these time-points were identified (**Table 5.10**).

A comparison of the within group change in BMI (paired t-test) revealed no significant differences in the pair-wise comparisons.

Table 5.10 BMI and change in BMI

Time-point	Control	Low fibre	High fibre	*ANOVA p value*
BMI (kg/m^2): Mean (sd)				
n	53	52	54	
Start of Radiotherapy	28.4 (6.3)	27.8 (5.8)	28.0 (5.4)	0.866
End of Radiotherapy	28.2 (6.3)	27.4 (5.8)	27.8 (5.6)	0.782
BMI (kg/m^2): Mean (sd)				
n	53	52	54	
BMI change Start to end RT	-0.2 (1.1)	-0.4 (1.0)	-0.2 (0.8)	0.207

Key: sd: standard deviation, RT: radiotherapy *significant: p<0.05

5.10 Study intervention: palatability analysis

The Visual Analogue Scale (VAS) used to measure the palatability of the fibre intervention is given in Appendix 2, item 4. Responses on the 150 mm scale in response to the question 'how palatable did you find the change in diet' ranged from 0 mm ('much worse than my normal diet') to 150 mm ('much better than my normal diet'), with a mid-point answer at 75 mm ('no different to my normal diet').

The median (range) VAS score for the 40 patients in the low fibre group who completed the scale was 78.5 mm (7 – 146) and for the 38 patients in the high fibre group who completed the scale it was 78.0 mm (5 – 150) indicating little difference, but wide variations in individual responses between the two groups.

5.11 Study intervention: researcher contact time

Analysis of the median (range) interview time in minutes with the study dietitian revealed that the contact time was similar for all groups. In the control group (53 with evaluable data) the average (range) time for each study interview was 16.5 (11.2 – 36.3) minutes, in the low fibre group (n=49) it was 18.6 (8.8 – 31.4) minutes and in the high fibre group (n=38) it was 18.1 (10 – 34.2) minutes.

The average number of interviews conducted per patient was four, comprising one enrolment interview, one exit interview (end of study) and a minimum of two on-treatment interviews for the collection of study measurements.

5.12 Ease of use of interventional tools

Forty four patients (low fibre: 22; high fibre: 22) completed the Ease of Use questionnaire of the Fibre in Foods booklet. These respondents had a mean (sd) age 61.8 (12.7) years, females: 61; males: 39. Responses to the questionnaire are detailed in **Table 5.11.**

All patients found the design and layout of the booklet 'very easy' or 'quite easy' to follow, with 48% of patients reporting that it was 'very easy' to follow. Responses were similar in the low and high fibre groups. A large proportion of patients (>85% for both low and high fibre groups) also reported that they would recommend the booklet to others wanting to estimate their fibre intake.

Seventy percent of patients reported that they were 'mostly' able to find the fibre content of all the foods they consumed. Several reported difficulties with finding the fibre content of festive foods (around the Christmas period) and also ethnic items especially those from the Indian sub-continent. Where patients reported comments regarding which foods they experienced most difficulties with estimating fibre content, cereals and breads were most commonly cited.

Fifty percent of patients reported that they didn't feel the need to weigh food items and the remaining 50% who reported that they often or occasionally needed to weigh items to estimate fibre content were equally divided amongst both high and low fibre groups. About one third of patients reported using food labels to supplement booklet information although the majority needed to use them for less than 50% of the time.

Sixty six percent of patients returned fibre exchange diaries (**Table 5.1**) and many reported finding these a useful aid to estimating their daily fibre intake.

Table 5.11 Responses to questionnaire in 44 patients: Ease of use of Fibre in Foods booklet

Questionnaire section / responses	*ALL*	*Low fibre*	*High fibre*
1. Design / organisation: How easy was the Fibre in Foods booklet to use?	*n (%) of group agreeing with each response*		
Very easy	21 (48)	10 (45)	11 (50)
Quite easy	23 (52)	12 (55)	11 (50)
Undecided	-	-	-
Quite difficult	-	-	-
Very difficult	-	-	-
2. Would you recommend the booklet to others to estimate fibre intake?			
Definitely yes	39 (89)	20 (91)	19 (86)
Maybe yes	5 (11)	2 (9)	3 (14)
Undecided	-	-	-
Maybe no	-	-	-
Definite no	-	-	-
3. Were you able to find the fibre content of all the foods you ate?			
Yes, always	11 (25)	5 (23)	6 (27)
Yes, mostly	31 (70)	15 (68)	16 (73)
Undecided	2 (5)	2 (9)	-
No, partly	-	-	-
No, never	-	-	-
4. Did you weigh food items?			
Yes, often	8 (18)	4 (18)	4 (18)
Occasionally	15 (34)	7 (32)	8 (36)
Never	21 (50)	11 (50)	10 (46)
5. Did you have to use food labels in addition to booklet information?			
Yes, more than 50% of the time	5 (11)	-	5 (23)
Yes, but less than 50% of the time	20 (45)	12 (55)	8 (36)
No, never as I did not have time	4 (9)	2 (9)	2 (9)
No, never as I did not need to	15 (35)	8 (36)	7 (32)

5.13 Discussion of nutritional findings

In this open label, nutritional interventional trial, confidence that a robust intervention was achieved was critical to the validity of the clinical and nutritional results. There are a number of factors which might have confounded outcomes. Neither the setting of fibre targets nor the measurement of daily fibre intake is straightforward. With respect to the setting of daily fibre targets, a bespoke guideline booklet was developed for use in the study. The design of the booklet was a balance between on the one hand,

including the maximum possible number of commonly-consumed fibre-containing items so that fibre intake could be assessed as accurately as possible, whilst on the other hand, not including so many items that recording of daily fibre intake became so time-consuming that poor compliance would result. All forty-four patients questioned regarding their use of the booklet reported that they found it either 'very easy' or 'quite easy' to use and said that they would recommend it to others wishing to estimate their daily fibre intake (**Table 5.11**). So, in this respect, the booklet succeeded in its aim.

However, the estimation of fibre intake is quite complex for patients and further complicated by the different definitions of fibre in use today. A decision was taken in the current study to base the daily fibre targets on the NSP content of foods and to use these values for defining the fibre content of foods in the guideline booklet. This was because daily reference values in the UK for fibre intake (albeit for healthy individuals) have been defined using the Englyst (NSP) method of analysis. Further, the dietary analysis software chosen for use in the study (Dietplan) has as its main reference source the UK Nutrient Databank. This database lists the fibre content of all foods it contains as g NSP but does not comprehensively (i.e. for all foods) include fibre content derived using other methods of analysis (e.g. Southgate estimates based on the AOAC methods).

Patients in the interventional groups were provided with low or high fibre exchange diaries so that they could keep a record of daily self-estimated fibre consumption. However, UK food labelling is a source of potential confusion for patients. The nutritional breakdown of foods appearing on food packets is based on the fibre content of foods measured using the AOAC method of analysis which tends to result in higher values of fibre (1.6 x NSP) per 100 g food than the Englyst NSP method. When questioned as to their use of food labels (**Table 5.11**) 45% of the sample of 44 patients questioned did use food labels to help estimate their fibre content. Thus, in estimating their daily fibre intake, heavy reliance of food labels may have tended to over-estimate intake, whilst exclusive use of the guideline booklet to estimate the fibre content of the same foods would have resulted in lower values. Pre-trial validation of the use of the guideline booklet in comparison to use of food labels may have helped to shed

some light on possible differences. However, such a study was not possible within the time-frame and resources available.

The assessment of fibre intake in all trial groups was achieved using 7 day food diaries. Patients were asked to record intake of food and drink and describe this in terms of household measures rather than weighing items. While 7 days is sufficient to take account of daily fluctuations in nutrient intake, the method is subject to error as information on portion sizes (e.g. photographic material) was not provided. The percentage return of food diaries was 92% for week one of treatment and 81% for the final week of treatment with the analysis of nutrient intake based on a final 127 paired diaries. It could be argued that a robust intervention was achieved and that statistically different intakes of fibre were obtained between groups at both time-points.

However, clinically, the differences in fibre intake were relatively small. During week one, the low fibre group consumed -3.3g NSP / day less than the control group, the high fibre group consumed 3.6 g NSP / day more than the control group, and the difference in intake between the high and low fibre groups was 6.9 g NSP / day. During the final week of radiotherapy, the low fibre group consumed -3.3g NSP / day less than the control group, the high fibre group consumed 3.5 g NSP / day more than the control group, and the difference in intake between the high and low fibre groups was 6.8 g NSP / day.

Whilst a differential of 6.9 and 6.8 g NSP / day was maintained between the high and low fibre groups at week one and the final week of radiotherapy respectively, it is not clear whether this was enough to effect a difference. It is unclear why a significant difference in the change in IBDQ-B was observed between the high fibre and control groups and not between the high and low fibre groups. Figures 5.3 and 5.4 (horizontal floating bars representing the mean intake and mean ±1sd) illustrate the substantial overlap of intake at both time-points between groups (**Table 5.12**). The 80% cut-off for compliance in both high and low fibre groups is depicted on these figures.

Figure 5.3 Mean ± 1sd fibre intake: week one of radiotherapy

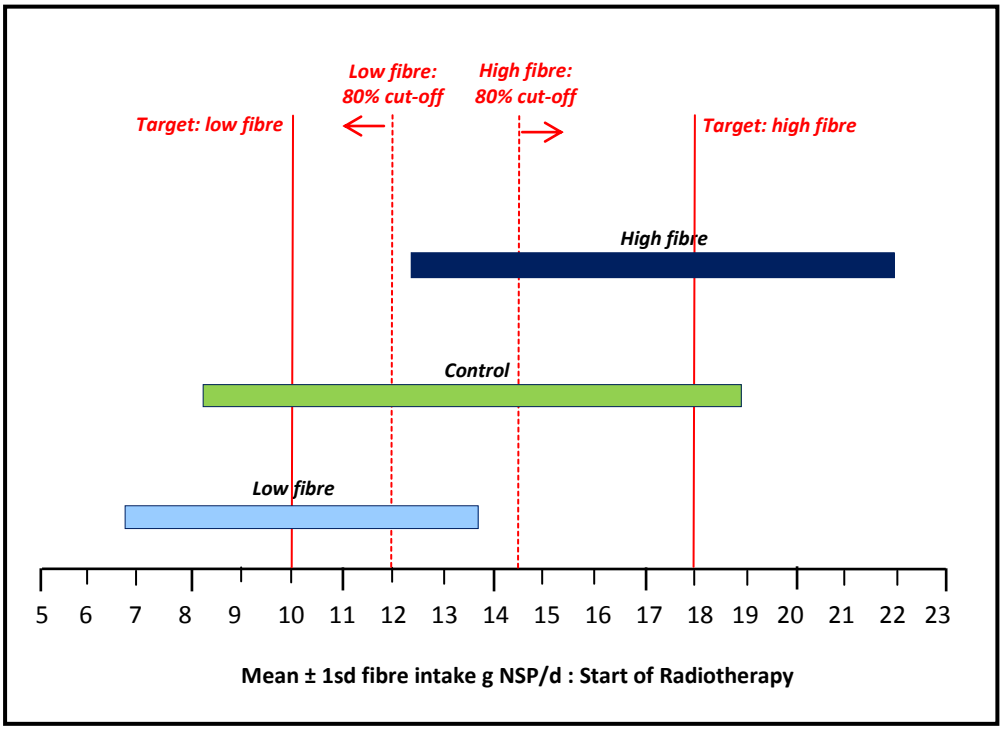


Figure 5.4 Mean ± 1sd fibre intake: final week of radiotherapy

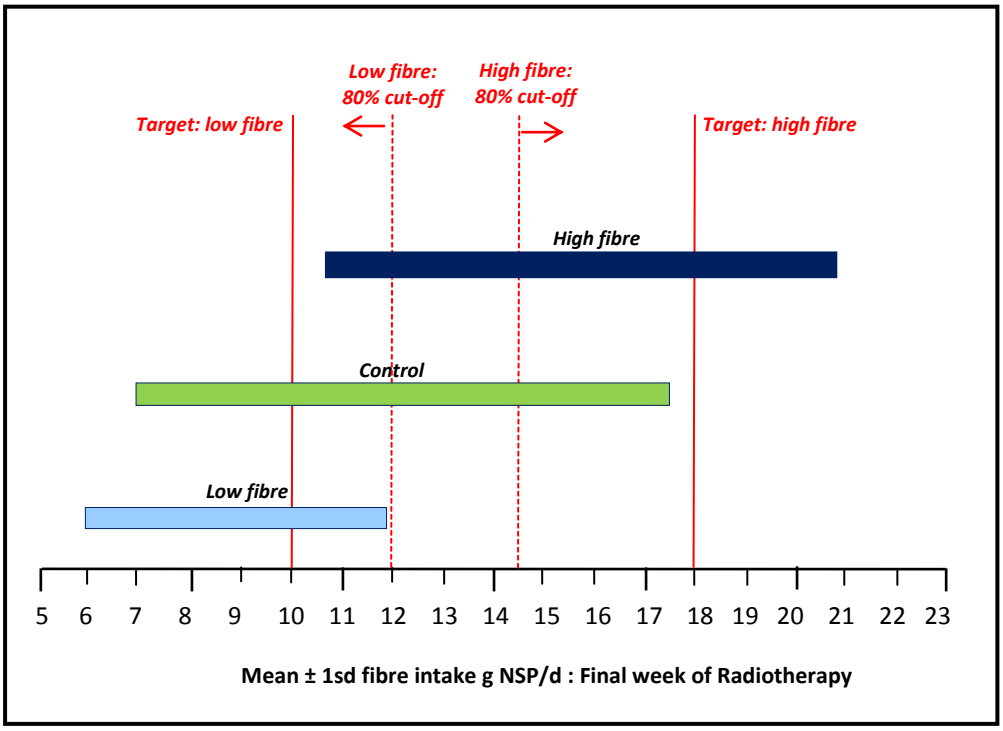


Table 5.12 Mean ± 1sd fibre intake: week one and final week of radiotherapy

	Control	Low fibre	High fibre
Fibre intake (g NSP / day) : week one of radiotherapy			
Mean -1sd	8.3	6.8	12.4
Mean	13.6	10.2	17.1
Mean + 1sd	18.9	13.7	21.9
Fibre intake (g NSP / day) : final week of radiotherapy			
Mean -1sd	7.0	5.9	10.6
Mean	12.2	8.9	15.7
Mean + 1sd	17.4	11.9	20.8

The analysis of compliance showed that during week one, 77% and 79% of patients complied to within 80% of their fibre target. During the final week of radiotherapy, compliance (to within 80%) was higher in the low fibre group (83%) compared to that in the high fibre group (63%). A per protocol ANOVA in those patients who achieved 80% compliance with fibre target revealed no significant difference in the change in IBDQ-B score between the low and high fibre groups between baseline and end of RT as in the main analysis (p=0.395). A comparison of scores at both time-points for the main analysis and per protocol (80% compliance cut-off) is given in Table **5.13**.

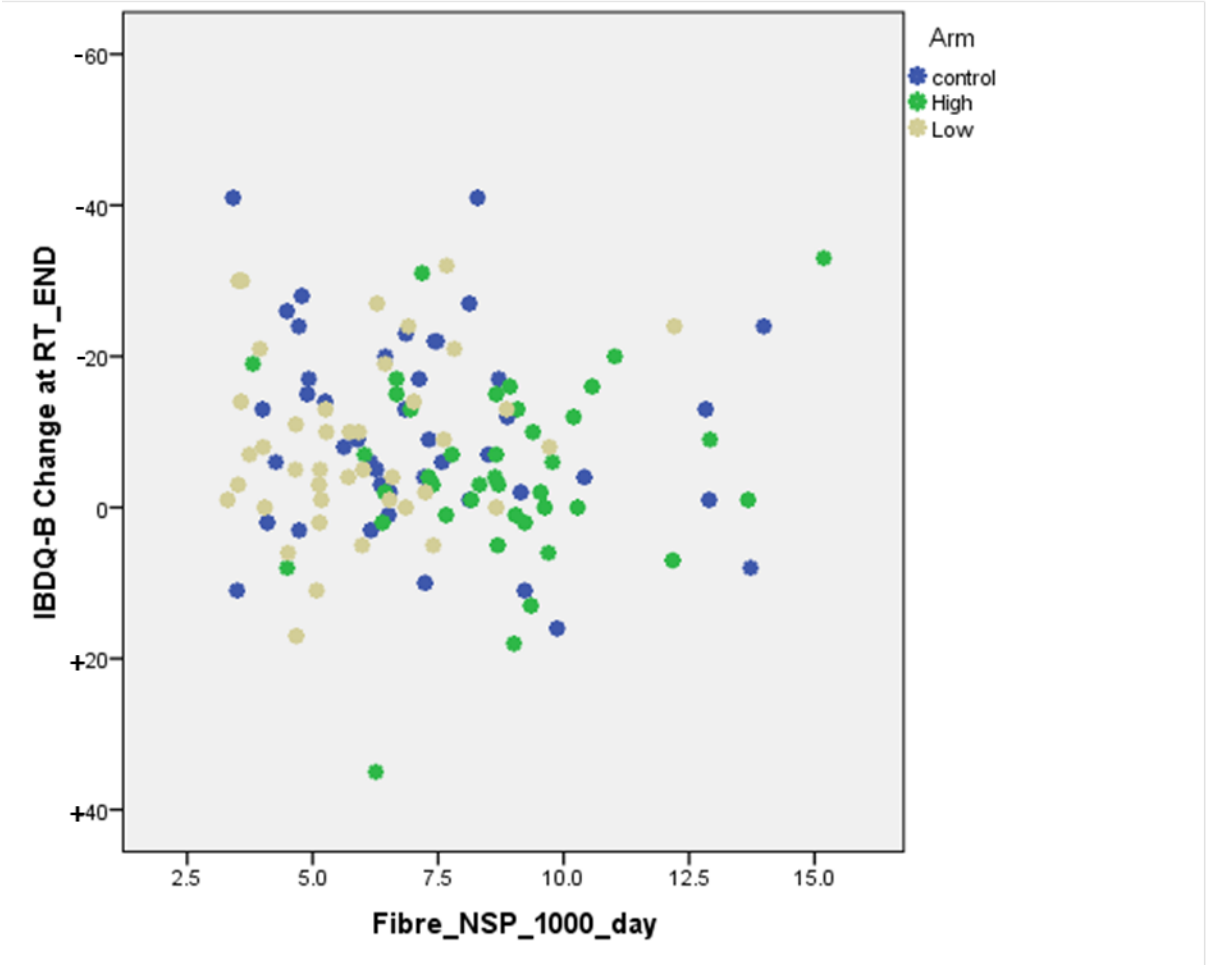
Table 5.13 Change in IBDQ-B and IBDQ scores: main *versus* per protocol analysis

Measurement Analysis method	Low fibre	High fibre
IBDQ-B - change in score Baseline to end RT: Mean (sd)		
n	52	54
IBDQ-B main analysis	-7.4 (11.6)	-3.1(13.0)
n	34	27
IBDQ-B per protocol analysis	-7.5 (10.9)	-5.0 (11.8)
IBDQ - change in score Baseline to end RT: Mean (sd)		
n	52	54
IBDQ main analysis	-17.2 (26.5)	-6.7 (30.2)
n	34	27
IBDQ per protocol analysis	-16.9 (26.7)	-9.7 (22.6)

Given the wide range of fibre intake amongst the trial groups, an analysis of change in IBDQ-B versus quartiles of fibre intake may be useful. An exploratory analysis of the

change in IBDQ-B (baseline – end RT) versus fibre intake (g NSP / 1000 kcal) reveals no obvious patterns (**Figure 5.5**).

Figure 5.5 Scatter plot: change in IBDQ-B versus fibre intake in final week of RT



Two researchers extracted 7 day diary data and this could have been a source of error. However, analysis of inter-researcher variation revealed the lack of a systematic variation between researchers in the estimation of energy or fibre intake and reasonable agreement. One advantage of using two researchers, additional to the author (LW) to extract food diary data (apart from halving the time required to undertake this activity) is that they can be blinded to interventional group. Provision of adequate training in the use of Dietplan software and standardisation of approach are essential, both of which occurred. However, despite these checks and balances in approach, the quality of the data obtained regarding fibre intake in this study is reliant on the quality of the recording of fibre intake by patients themselves and it is probable

that there is considerable inter-patient variation in the quality of self-estimation of fibre intake. In the last decade, a plamsa biomarker of dietary fibre intake, alkylresourcinols 'ARs' (and its plasma and urinary metabolites) has been proposed and used successfully for the assessment of wholegrain and rye intake[253]. ARs (3,5-dihydroxy-phenolic lipids) are found in appreciable quantities in wholegrain wheat, rye and barley cereal products with only a trace in corresponding refined alternatives. However, wide inter-individual variation exists in the levels of this biomarker in response to intake and its use in specific clinical cohorts remains untested[253]. Further, how well ARs correlate with total fibre intake from all dietary sources is unknown and at present their use may be more valuable in studies using supplemental fibre interventions based on known quantities of wheat, rye and barley substrates than in dietary based interventions such as that used in the present study.

The intervention had no adverse effect on body weight or BMI with no significant differences between groups identified in the change in body weight or BMI at the end of treatment. In fact, the finding in this study that the high fibre intervention had a positive effect on total energy intake in the final week of radiotherapy in comparison to the control group is in keeping with recent research. Two recent reviews have challenged the long-held view that fibre leads to increased satiety and causes reduced energy intake[251 252]. In the review by Wanders[251], effects of fibre on energy intake and body weight were small and distinct dose-response relationships were not observed. In the review by Clark[252], neither type of dietary fibre or dose was related to satiety or food intake.

Further, a significant difference in protein intake was also identified during the final week of radiotherapy between the high and low fibre groups with the high fire group consuming a mean 14.6 g protein/day more than the low fibre group. Other authors have found that dietary advice based on manipulation of the normal diet is more effective than supplementation alone or standard care in improving total energy and protein intake in patients receiving pelvic radiotherapy both in the acute setting and over longer-term follow-up. A positive relationship between individualized nutritional intervention and quality of life has been demonstrated with 'early intervention and sensible partnerships with patients being key to success'[248].

An exploratory analysis of micronutrient intake identified several specific micronutrients where daily intake was less than the UK RNI. The significance of this finding on micronutrient status was not examined and the study was not powered to detect differences in these nutritional endpoints. For the future, deficiencies in intake identified in week one of treatment could be usefully corrected with judicious supplementation if longer-term risk of ongoing depletion and reduced intake existed.

In summary, it is concluded that the fibre intervention was a robust intervention and that differences in the clinical outcomes in favour of the high fibre group (**Chapter 4**) reflect, in part, differing fibre intake. In the trial, patients demonstrated that they were willing and able to follow detailed dietary advice for the duration of radical radiotherapy treatment. The time taken to develop appropriate and acceptable interventional tools was rewarded with a high rate of return for study documentation.

The reason for the lack of a significant difference between the high and low fibre groups for the change in IBDQ-B and IBDQ scores remains unclear and may be influenced by treatment or patient-related factors discussed in the preceding chapter. As far as possible the interventional design used in the present study attempted to control for a wide range of issues which may confound outcomes and in comparison to many of the studies identified in the two systematic reviews, achieved this aim.

One final point of discussion is the possible influence of the nature and purpose of professional dietetic input during treatment. Whilst the trial achieved standardised contact time between patients in all groups with the principal researcher (LW) the lack of detailed discussion regarding fibre intake in the control group patients may have left them feeling less well supported in making 'appropriate' dietary choices.

Dietary manipulation, as illustrated by the number of patients citing this as a reason for declining study entry (36%), is clearly an important issue. It is speculative to suggest that dietetic input alone may have an effect although other researchers have hinted at such. In a recent Cochrane review, dietetic input, using mixed interventions, were seen to be better than no intervention to prevent or reduce onset of treatment-induced

diarrhea[129]. In the planned update of this review it is hoped that the results of the fibre study can be added to the sum of evidence although an agreed definition of treatment-induced diarrhea will first need to be agreed.

CHAPTER 6

Discussion

6.1 Summary of findings

The work undertaken in this thesis was carried out to test the hypothesis outlined below:

'***Dietary fibre can prevent or reduce gastrointestinal inflammation in diseases such as inflammatory bowel disease and may be a simple cost-effective nutritional intervention to reduce or prevent acute symptoms during pelvic radiotherapy. Its mechanism of action is via production of anti-inflammatory fermentation products short chain fatty acids and through beneficial effects of dietary fibre on stool frequency and form'.***

I am able to only partially accept the first part of this hypothesis. Whilst increased (supplemental) fibre showed a modest benefit (4/23 studies) for disease outcomes in IBD, the results of the Fibre Study RCT showed that both a high and low fibre diet intervention had a positive effect in reducing bowel symptoms compared to the control group, with the difference between the high fibre and control groups reaching statistical significance (p=0.007). The mechanism(s) through which fibre intake is exerting these effects is not clear but may indicate that there are possibly differing, independent benefits of both high and low fibre intake. Evidence that beneficial effects are mediated through SCFA is lacking and thus I cannot accept the second part of the hypothesis. However, the results of the RCT suggest that, contrary to previously held views, increased dietary fibre does not necessarily have an adverse impact on stool frequency or form although the possible confounding effects on outcomes of increased use of anti-diarrhoeal medication in the high fibre group cannot be ignored.

The systematic review of the efficacy of fibre in IBD identified a benefit of increased dietary fibre intake on disease outcomes for patients in remission and with active disease in ulcerative colitis (3/10 studies), and in patients in remission with pouchitis (1/1 study). Although no studies reported increased fibre intake to be of benefit on disease outcomes in Crohn's disease (0/12 studies) and only one study reported a negative effect of increased fibre intake, three reported equivalence of low and high fibre intake, a finding that has some resonance with the outcome of the RCT. Meta-

analysis was not possible due to the widely varying study designs and endpoints employed.

IBD presents a model of gastrointestinal inflammation the pathophysiology of which shows many similar features to acute radiation-induced toxicity. Thus, finding a benefit of fibre in IBD was an important first step to justify an intervention in patients receiving pelvic radiotherapy, provided no previous studies had been undertaken. Unfortunately few studies identified in the systematic review of fibre and IBD combined clinical and physiological endpoints and thus possible mechanisms regarding the efficacy of dietary fibre could not be critically examined. However, many studies reported within-group benefits of increased fibre intake including positive effects on short chain fatty acids (SCFA), beneficial effects on microbiota species and reduction in pro-inflammatory cytokines. The studies also provided useful data with respect to differing interventional methodologies.

In view of the modest but promising effects of fibre in patients with IBD a second systematic review was conducted to establish if any evidence for the efficacy of manipulating dietary fibre intake existed in patients undergoing pelvic radiotherapy. Very few studies were identified (only four RCTs) and these varied widely in design and endpoints. Whilst the possible efficacy of increased or manipulated fibre intake was hinted at in these studies it was concluded that the sum of evidence was weak and that there was adequate justification for conducting a properly powered RCT. The aim of this RCT would be to investigate the benefit of manipulating dietary fibre in patients receiving pelvic radiotherapy.

Important lessons were learned from conducting the second systematic review. Of the four studies identified for inclusion in the review, all manipulated fibre in addition to imposing other dietary restrictions making it difficult to discern whether the effects observed were due to fibre or some other dietary component. Few measured compliance with intervention or attempted to measure background dietary intake. No studies combined clinical and physiological outcomes. Two studies addressing the efficacy of fibre for the prevention of treatment-induced diarrhoea were combined in meta-analysis. However, both used different tools for assessing the incidence of

treatment-induced diarrhoea and although one attempted to define diarrhoea using parameters of both stool frequency and form, this definition was not validated. Although not statistically significant, a slight benefit was identified for fibre intervention: Risk Ratio 0.75 (95% CI: 0.56 – 1.01).

An interesting distinction between the two systematic reviews was that many of the studies conducted in IBD patients used supplement interventions, certainly the ones that showed a benefit in ulcerative colitis used this interventional strategy whilst those conducted in pelvic radiotherapy patients used dietary restrictions as secondary interventions in addition to the primary (supplement) intervention. The one study that did use a dietary intervention as the primary strategy in patients receiving pelvic radiotherapy was unable to quantify dietary fibre intake as the food frequency questionnaire devised for the study contained no information on portion sizes.

The lack of robust evidence of the efficacy of fibre in the pelvic radiotherapy setting, justified and led to the conducting of a new RCT, the 'Fibre study'. The design of this study was informed from the findings of the two systematic reviews and was powered to a specific clinical endpoint (symptom scores) but included a physiological outcome measure, SCFA and patient-reported data on daily stool frequency and form. A dietary intervention for the manipulation of fibre intake was chosen for palatability and physiological reasons. In the design of the interventional tools for the RCT, considerable attention was paid to the design and interventional strategy to enable patients to comply with interventional dietary advice. Our unit had previously demonstrated that patients in this setting are willing and able to follow dietary advice for the duration of radiotherapy. However, we had also seen that patients' own perceptions can quickly over-rule research-based interventional targets resulting in a lack of differential between groups in the nutrient under test.

The Fibre study identified a statistically significant benefit for a high fibre intervention and a non-significant benefit for a low fibre intervention, both in comparison to the control group for the change (worsening) in symptom scores, measured using the change in IBDQ-B scores between start and end of radiotherapy. This finding leads to the conclusion that both high and low fibre interventions may confer befit with respect

to the onset or severity of treatment-induced gastrointestinal symptoms compared to no intervention. It is possible that different, independent mechanisms are operating to confer benefit for the high and low fibre interventions compared to the no intervention group. It is also possible that dietitian-led advice, or perhaps increased awareness of fibre intake, results in a beneficial placebo-type effect in this therapy setting. In this context, it is interesting that the high fibre intervention also resulted in statistically significantly improved quality of life scores, measured using the IBDQ between start and end of radiotherapy compared to the control group. Once again the low fibre intervention also showed benefit in this respect in comparison to the control group but failed to achieve statistical significance.

With respect to nutritional intake and status, randomisation to the high fibre group did not adversely affect total energy intake, whilst a within-group analysis revealed that the control group had a significantly reduced total energy and protein intake between week one and the final week of treatment and the low fibre group had a significantly reduced protein intake and borderline significantly reduced total energy intake. In contrast, the high fibre group experienced no significant change in total energy or protein intakes between these time-points.

In summary, the fibre study recruited to target, was subject to a very low drop-out rate and enjoyed a high rate of return of study data. Whilst it has not unequivocally demonstrated that previously-given advice to reduce dietary fibre during radiotherapy is inappropriate, neither has it proven that increased dietary fibre intake during pelvic radiotherapy is significantly better than a low fibre regimen. However, it has demonstrated that dietitian-led advice regarding fibre intake during radiotherapy treatment appears to be helpful.

Further investigation of the possibly differing mechanisms of protection conferred by low *versus* high dietary fibre intakes would be interesting to examine. A thorough examination of this question would benefit from the use of biological markers (if available) to monitor toxicity, markers (if available) to confirm or validate self-reported dietary fibre intake and the capture of data regarding the proportion of the fibre intervention provided by soluble (readily fermentable) versus insoluble (less well

fermented) fibre fractions. Finally, in future work, it is recommended that habitual fibre intake be recorded prior to fibre manipulation. Unfortunately this was not feasible in the Fibre study. However, change in fibre intake resulting from randomisation (e.g. to a higher or lower amount) may effect gastrointestinal function and thus outcomes. Therefore, adequate time for gastrointestinal acclimatisation should be built-in to future study time-lines.

6.2 Answers to research questions

In answer to the research questions posed earlier in this thesis it has been demonstrated that:

- Manipulation of dietary fibre intake can be a useful intervention in the treatment and management of gastrointestinal inflammation in diseases such as IBD and may have a role in the prevention of radiation-induced gastrointestinal toxicity, although the assessment of toxicity using symptom indices is acknowledged as imperfect.

- Advice to consume a high fibre diet may reduce the severity (or incidence) of new onset acute radiation-induced gastrointestinal toxicity during pelvic radiotherapy when compared to no dietary advice. However, advice to consume a low fibre diet may also be helpful indicating that dietary advice regarding fibre intake may in itself be a useful intervention.

- Dietary fibre manipulation may affect the concentration or proportions of faecal SCFA during pelvic radiotherapy treatment although evidence from the Fibre study is inconclusive and too limited to be extrapolated to the randomised cohort.

- Dietary fibre manipulation does not adversely affect stool frequency, stool form or incidence of loose stool during pelvic radiotherapy although use of anti-diarrhoeal medication may mask these effects.

- Patients can comply with high or low fibre dietary interventional advice for the duration of pelvic radiotherapy. It is probable that compliance is enhanced by the production of accessible interventional tools. Compliance to 100% of target is not easily attainable.

- Adherence to a high fibre target intake does not compromise body weight, body mass index (BMI), total energy intake or micronutrient intake.

6.3 Future research activities

The fibre study has raised some interesting issues with respect to the provision of dietary advice to increase or decrease fibre intake during pelvic radiotherapy. However, the scope of research outlined in the original trial protocol includes the capture of additional data which it is planned will answer further questions.

In view of the important relationship between acute and late gastrointestinal toxicity one very important late primary endpoint that is yet to be analysed is:

- An analysis of the difference between trial groups in the mean change in IBDQ-B score between the start and end of radiotherapy and score at one year. This will be done using paired scores from patients with scores at acute and late (one year) time-points.

Data in respect of this question are currently maturing and it is anticipated that the analysis will be complete early in 2015.

Although the Fibre study was not powered to answer the following research questions, an exploratory analysis of the following issues is also being carried out and will be also be reported in the near future:

- What effect has the fibre intervention had on the level of bowel toxicity experienced? Specifically has the intervention offered any benefits that can be detected between groups in terms of the anticipated levels of gastrointestinal toxicity versus volume of bowel treated and radiotherapy dose received?

- What is the economic burden to patients of managing gastrointestinal symptoms arising during pelvic radiotherapy?

- Is there an economic burden to patients associated with attempting to follow the interventional fibre targets in the Fibre study?

Aside from the Fibre study, it is hoped that a more thorough investigation of the role of SCFA in this setting can be conducted. This investigation should include the use of symptom scoring measures so that with adequate statistical powering it may be possible to determine whether these physiological markers can be associated with more commonly used subjective outcomes.

6.4 Implications of findings for healthcare professionals

It is clear that many patients actively seek dietary advice during treatment and welcome prescriptive advice as being empowering in an otherwise highly technical treatment environment into which they have very limited input. However, given the outcomes of the Fibre study, it is difficult to recommend what definitive advice should be given to patients in this setting.

Given that statistically significant benefits were shown for patients asked to consume a high fibre intake, it is tempting to suggest that all patients increase their fibre intake during treatment. However, no clear benefit was seen for a high fibre intake in comparison to a low fibre intake and thus advice for all patients to increase fibre may not be appropriate as low fibre may also offer some benefit or may benefit certain individuals.

One strategy could be to recommend that all patients follow their habitual fibre intake but are provided with access to a named, registered dietitian who can provide advice on specific aspects of fibre intake or diet when required and monitor nutritional status and intake. The no intervention (i.e. habitual fibre intake) group experienced the worst treatment-induced symptoms, most reduction in quality of life scores and had a significantly reduced total energy and protein at the end of treatment compared to the

start. It is possible that enhanced, individualised dietary care alone could be helpful in guarding against these outcomes. Such a strategy has resource implications and will require further discussion prior to implementation if deemed appropriate.

The results of the one-year follow-up are awaited and may yet yield further evidence of the efficacy of high fibre intake in the acute setting on late outcomes. However, results will need to be interpreted with caution since loss to follow-up will alter the composition of groups between treatment and the one year follow-up time points.

6.5 Personal reflection

The Fibre study has been a resource-intensive study. The fact that it has largely been conducted by a single individual (LW) masks the fact that without the input of many other allied health professionals and clinicians, and the support of data management and statistical personnel, the study could not have been accomplished.

All research work requires a champion or possibly champions, firstly to have the vision to generate credible and necessary hypotheses and secondly to ensure that the work is carried out to meet the exacting design and governance requirements. Research cannot be conducted in isolation and true multi-disciplinary working must be the key to success.

Funding for research is competitively sought and completion is fierce. Once obtained, there is a clear responsibility of all involved not only to each other as healthcare professionals but to patients. The work conducted in this thesis is to benefit patients not researchers.

7. References

1. Tobias J, Hochhauser D. The modern management of cancer: an introductory note. *Cancer and its Management*. Chichester, UK: Wiley Blackwell, 2010:1-6.

2. Ellis H, Logan BM, Dixon AK. *Human Sectional Anatomy.* 2nd Edition ed. London: Hodder Arnold, 2001.

3. CRUK CRU. United Kingdom Cancer Incidence 2011, Summary Counts, January 2014 CRUK, 2014:UK Cancer Incidence 2011, Summary Counts.

4. Hoskin P. Introduction. In: Hoskin P, editor. *Radiotherapy in Practice. External Beam Therapy.* Oxford UK: Oxford University Press, 2006:1-5.

5. Radiologists RCo. Equipment, workload and staffing for radiotherapy in the UK 1997 - 2002. London, UK: Royal College of Radiologists, 2003.

6. Khalid U, McGough C, Hackett C, Blake P, Harrington KJ, Khoo VS, et al. A modified inflammatory bowel disease questionnaire and the Vaizey Incontinence questionnaire are more sensitive measures of acute gastrointestinal toxicity during pelvic radiotherapy than RTOG grading. *Int J Radiat Oncol Biol Phys* 2006;64(5):1432-41.

7. Delaney G, Jacob S, Featherstone C. The role of radiotherapy in cancer treatment. Estimating optimal utilisation from a review of evidence-based guidelines. *Cancer* 2005;104(6):1129-37.

8. Henson CC, Andreyev HJ, Symonds RP, Peel D, Swindell R, Davidson SE. Late-onset bowel dysfunction after pelvic radiotherapy: a national survey of current practice and opinions of clinical oncologists. *Clinical oncology (Royal College of Radiologists (Great Britain))* 2011;23(8):552-7.

9. Wedlake LJ, Andreyev HJ. Manipulating the consequential effect: an alternative approach to reducing pelvic radiation disease other than dose reduction. *Current opinion in supportive and palliative care* 2011;5(1):25-8.

10. Griffths S. *Radiotherapy: Principles to Practice. A Manual for Quality in Treatment Delivery*. 2nd Edition ed. Leeds: Churchill Livingstone, 1995.

11. Taylor A, Powell MEB. Uterus. In: Hoskin P, editor. *Radiotherapy in Practice. External Beam Radiotherapy*. New York: Oxford University Press, New York, 2006:235-58.

12. McNair HA, Wedlake L, Lips IM, Andreyev H, Van Vulpen M, Dearnaley D. A systematic review: Effectiveness of rectal emptying preparation in prostate cancer patients. *Practical Radiation Oncology* 2014;In press.

13. Andreyev HJ, Wotherspoon A, Denham JW, Hauer-Jensen M. Defining pelvic-radiation disease for the survivorship era. *Lancet Oncol* 2010;11(4):310-2.

14. Andreyev HJ, Davidson SE, Gillespie C, Allum WH, Swarbrick E. Practice guidance on the management of acute and chronic gastrointestinal problems arising as a result of treatment for cancer. *Gut* 2012;61(2):179-92.

15. Henson CC, Davidson SE, Lalji A, Symonds RP, Swindell R, Andreyev HJ. Gastrointestinal symptoms after pelvic radiotherapy: a national survey of gastroenterologists. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer* 2012;20(9):2129-39.

16. Denham JW, Hauer-Jensen M, Peters LJ. Is it time for a new formalism to categorize normal tissue radiation injury? *Int J Radiat Oncol Biol Phys* 2001;50(5):1105-6.

17. Bentzen SM. Preventing or reducing late side effects of radiation therapy: radiobiology meets molecular pathology. *Nature reviews. Cancer* 2006;6(9):702-13.

18. Denham JW, Hauer-Jensen M. The radiotherapeutic injury--a complex 'wound'. *Radiother Oncol* 2002;63(2):129-45.

19. Dorr W, Hendry JH. Consequential late effects in normal tissues. *Radiother Oncol* 2001;61(3):223-31.

20. Hovdenak N, Fajardo LF, Hauer-Jensen M. Acute radiation proctitis: a sequential clinicopathologic study during pelvic radiotherapy. *Int J Radiat Oncol Biol Phys* 2000;48(4):1111-7.

21. Andreyev J. Gastrointestinal symptoms after pelvic radiotherapy: a new understanding to improve management of symptomatic patients. *Lancet Oncol* 2007;8(11):1007-17.

22. Hovdenak N, Karlsdottir A, Sorbye H, Dahl O. Profiles and time course of acute radiation toxicity symptoms during conformal radiotherapy for cancer of the prostate. *Acta Oncol* 2003;42(7):741-8.

23. Larsen A, Bjorge B, Klementsen B, Helgeland L, Wentzel-Larsen T, Fagerhol MK, et al. Time patterns of changes in biomarkers, symptoms and histopathology during pelvic radiotherapy. *Acta Oncol* 2007;46(5):639-50.

24. Wedlake L, McGough C, Hackett C, Thomas K, Blake P, Harrington K, et al. Can biological markers act as non-invasive, sensitive indicators of radiation-induced effects in the gastrointestinal mucosa? *Aliment Pharmacol Ther* 2008;27(10):980-7.

25. Hennekens CH, Buring JE. *Epidemiology in Medicine*. Boston and Toronto: Little , Brown and Comapny, 1987.

26. Benton B, Norton C, Lindsay JO, Dolan S, Andreyev HJ. Can Nurses Manage Gastrointestinal Symptoms Arising from Pelvic Radiation Disease? *Clinical oncology (Royal College of Radiologists (Great Britain))* 2011.

27. Wedlake L, Thomas K, McGough C, Andreyev HJ. Small bowel bacterial overgrowth and lactose intolerance during radical pelvic radiotherapy: An observational study. *Eur J Cancer* 2008;44(15):2212-7.

28. Denton AS, Bond SJ, Matthews S, Bentzen SM, Maher EJ. National audit of the management and outcome of carcinoma of the cervix treated with radiotherapy in 1993. *Clinical oncology (Royal College of Radiologists (Great Britain))* 2000;12(6):347-53.

29. Ooi BS, Tjandra JJ, Green MD. Morbidities of adjuvant chemotherapy and radiotherapy for resectable rectal cancer: an overview. *Diseases of the colon and rectum* 1999;42(3):403-18.

30. Eifel PJ, Levenback C, Wharton JT, Oswald MJ. Time course and incidence of late complications in patients treated with radiation therapy for FIGO stage IB carcinoma of the uterine cervix. *Int J Radiat Oncol Biol Phys* 1995;32(5):1289-300.

31. Schultheiss TE, Lee WR, Hunt MA, Hanlon AL, Peter RS, Hanks GE. Late GI and GU complications in the treatment of prostate cancer. *Int J Radiat Oncol Biol Phys* 1997;37(1):3-11.

32. Wang CJ, Leung SW, Chen HC, Sun LM, Fang FM, Huang EY, et al. The correlation of acute toxicity and late rectal injury in radiotherapy for cervical carcinoma: evidence suggestive of consequential late effect (CQLE). *Int J Radiat Oncol Biol Phys* 1998;40(1):85-91.

33. Denham JW, O'Brien PC, Dunstan RH, Johansen J, See A, Hamilton CS, et al. Is there more than one late radiation proctitis syndrome? *Radiother Oncol* 1999;51(1):43-53.

34. Weiss E, Hirnle P, Arnold-Bofinger H, Hess CF, Bamberg M. Therapeutic outcome and relation of acute and late side effects in the adjuvant radiotherapy of endometrial carcinoma stage I and II. *Radiother Oncol* 1999;53(1):37-44.

35. Jereczek-Fossa BA, Jassem J, Badzio A. Relationship between acute and late normal tissue injury after postoperative radiotherapy in endometrial cancer. *Int J Radiat Oncol Biol Phys* 2002;52(2):476-82.

36. O'Brien PC, Franklin CI, Poulsen MG, Joseph DJ, Spry NS, Denham JW. Acute symptoms, not rectally administered sucralfate, predict for late radiation proctitis: longer term follow-up of a phase III trial--Trans-Tasman Radiation Oncology Group. *Int J Radiat Oncol Biol Phys* 2002;54(2):442-9.

37. Peters ST, Heemsbergen WD, van Putten WL, Slot A, Tabak H, Mens JW, et al. Acute and late complications after radiotherapy for prostate cancer: results of a multicenter randomized trial comparing 68 Gy to 78 Gy. *Int J Radiat Oncol Biol Phys* 2005;61(4):1019-34.

38. Vargas C, Martinez A, Kestin LL, Yan D, Grills I, Brabbins DS, et al. Dose-volume analysis of predictors for chronic rectal toxicity after treatment of prostate cancer with adaptive image-guided radiotherapy. *Int J Radiat Oncol Biol Phys* 2005;62(5):1297-308.

39. Heemsbergen WD, Peeters ST, Koper PC, Hoogeman MS, Lebesque JV. Acute and late gastrointestinal toxicity after radiotherapy in prostate cancer patients: consequential late damage. *Int J Radiat Oncol Biol Phys* 2006;66(1):3-10.

40. Zelefsky MJ, Levin EJ, Hunt M, Yamada Y, Shippy AM, Jackson A, et al. Incidence of late rectal and urinary toxicities after three-dimensional conformal radiotherapy and intensity-modulated radiotherapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2008;70(4):1124-9.

41. Glatstein E. The Omega on Alpha and Beta. *Int J Radiat Oncol Biol Phys* 2011;81(2):319-20.

42. Bentzen SM, Constine LS, Deasy JO, Eisbruch A, Jackson A, Marks LB, et al. Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC): an introduction to the scientific issues. *Int J Radiat Oncol Biol Phys* 2010;76(3 Suppl):S3-9.

43. Gulliford SL, Foo K, Morgan RC, Aird EG, Bidmead AM, Critchley H, et al. Dose-volume constraints to reduce rectal side effects from prostate radiotherapy: evidence from MRC RT01 Trial ISRCTN 47772397. *Int J Radiat Oncol Biol Phys* 2010;76(3):747-54.

44. Denham JW, Peters LJ, Johansen J, Poulsen M, Lamb DS, Hindley A, et al. Do acute mucosal reactions lead to consequential late reactions in patients with head and neck cancer? *Radiother Oncol* 1999;52(2):157-64.

45. Pinkawa M, Holy R, Piroth MD, Fischedick K, Schaar S, Szekely-Orban D, et al. Consequential late effects after radiotherapy for prostate cancer - a prospective longitudinal quality of life study. *Radiation oncology (London, England)* 2010;5:27.

46. Wedlake LJ, Thomas K, Lalji A, Blake P, Khoo VS, Tait D, et al. Predicting Late Effects of Pelvic Radiotherapy: Is There a Better Approach? *Int J Radiat Oncol Biol Phys* 2010.

47. Gulliford SL, Partridge M, Sydes MR, Andreyev J, Dearnaley DP. A comparison of dose-volume constraints derived using peak and longitudinal definitions of late rectal toxicity. *Radiother Oncol* 2010;94(2):241-7.

48. Manichanh C, Varela E, Martinez C, Antolin M, Llopis M, Dore J, et al. The gut microbiota predispose to the pathophysiology of acute postradiotherapy diarrhea. *The American journal of gastroenterology* 2008;103(7):1754-61.

49. Covington JA, Wedlake L, Andreyev J, Ouaret N, Thomas MG, Nwokolo CU, et al. The detection of patients at risk of gastrointestinal toxicity during pelvic radiotherapy by electronic nose and FAIMS: a pilot study. *Sensors (Basel, Switzerland)* 2012;12(10):13002-18.

50. Wedlake LJ, Silia F, Benton B, Lalji A, Thomas K, Dearnaley DP, et al. Evaluating the efficacy of statins and ACE-inhibitors in reducing gastrointestinal toxicity in patients receiving radiotherapy for pelvic malignancies. *Eur J Cancer* 2012;48(14):2117-24.

51. West CM, Davidson SE. Measurement tools for gastrointestinal symptoms in radiation oncology. *Current opinion in supportive and palliative care* 2009;3(1):36-40.

52. Andreyev HJN. Toxicity versus symptoms. Personal communication. London, 2014.

53. Gibson RJ, Bowen JM. Biomarkers of regimen-related mucosal injury. *Cancer treatment reviews* 2011;37(6):487-93.

54. Onal C, Kotek A, Unal B, Arslan G, Yavuz A, Topkan E, et al. Plasma citrulline levels predict intestinal toxicity in patients treated with pelvic radiotherapy. *Acta Oncol* 2011;50(8):1167-74.

55. Jakobsson S, Ahlberg K, Taft C, Ekman T. Exploring a link between fatigue and intestinal injury during pelvic radiotherapy. *The oncologist* 2010;15(9):1009-15.

56. Hille A, Rave-Frank M, Christiansen H, Herrmann MK, Kertesz T, Hermann RM, et al. Faecal calprotectin and lactoferrin values during irradiation of prostate cancer correlate with chronic radiation proctitis: results of a prospective study. *Scandinavian journal of gastroenterology* 2009;44(8):939-46.

57. Bowen JM, Newbold K, Blake P, Wild G, Egner W, Norman AR, et al. Do serum levels of eosinophil granule-derived protein change in patients undergoing pelvic radiotherapy? *Clinical oncology (Royal College of Radiologists (Great Britain))* 2005;17(5):382-4.

58. Lutgens LC, Deutz N, Granzier-Peeters M, Beets-Tan R, De Ruysscher D, Gueulette J, et al. Plasma citrulline concentration: a surrogate end point for radiation-induced mucosal atrophy of the small bowel. A feasibility study in 23 patients. *Int J Radiat Oncol Biol Phys* 2004;60(1):275-85.

59. Larsen A, Hovdenak N, Karlsdottir A, Wentzel-Larsen T, Dahl O, Fagerhol MK. Faecal calprotectin and lactoferrin as markers of acute radiation proctitis: a pilot study of eight stool markers. *Scandinavian journal of gastroenterology* 2004;39(11):1113-8.

60. Koc M, Taysi S, Sezen O, Bakan N. Levels of some acute-phase proteins in the serum of patients with cancer during radiotherapy. *Biological & pharmaceutical bulletin* 2003;26(10):1494-7.

61. Cengiz M, Akbulut S, Atahan IL, Grigsby PW. Acute phase response during radiotherapy. *Int J Radiat Oncol Biol Phys* 2001;49(4):1093-6.

62. Henson CC, Ang YS. Biomarkers of normal tissue toxicity after pelvic radiotherapy. *Current opinion in supportive and palliative care* 2012;6(1):33-40.

63. Lutgens LC, Lambin P. Biomarkers for radiation-induced small bowel epithelial damage: an emerging role for plasma citrulline. *World journal of gastroenterology : WJG* 2007;13:3033-42.

64. Crenn P, Vahedi K, Lavergne-Slove A, Cynober L, Matuchansky C, Messing B. Plasma citrulline: A marker of enterocyte mass in villous atrophy-associated small bowel disease. *Gastroenterology* 2003;124(5):1210-9.

65. Costa F, Mumolo MG, Bellini M, Romano MR, Ceccarelli L, Arpe P, et al. Role of faecal calprotectin as non-invasive marker of intestinal inflammation. *Digestive and liver disease : official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver* 2003;35(9):642-7.

66. Wedlake LJ, Khan K, Ahmedi B, Thomas K, Abraham D, Andreyev N, et al. Letter in response to article: a pilot study examining circulating interleukin-6 and transforming growth factor-beta levels during pelvic radiation therapy. *American journal of clinical oncology* 2013;36(1):102-3.

67. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). *Int J Radiat Oncol Biol Phys* 1995;31(5):1341-6.

68. Chen Y, Trotti A, Coleman CN, Machtay M, Mirimanoff RO, Hay J, et al. Adverse event reporting and developments in radiation biology after normal tissue injury: International Atomic Energy Agency consultation. *Int J Radiat Oncol Biol Phys* 2006;64(5):1442-51.

69. Rubin P, Constine LS, Fajardo LF, Phillips TL, Wasserman TH. RTOG Late Effects Working Group. Overview. Late Effects of Normal Tissues (LENT) scoring system. *Int J Radiat Oncol Biol Phys* 1995;31(5):1041-2.

70. Pavy JJ, Denekamp J, Letschert J, Littbrand B, Mornex F, Bernier J, et al. EORTC Late Effects Working Group. Late effects toxicity scoring: the SOMA scale. *Radiother Oncol* 1995;35(1):11-5.

71. Bentzen SM, Dorr W, Anscher MS, Denham JW, Hauer-Jensen M, Marks LB, et al. Normal tissue effects: reporting and analysis. *Seminars in radiation oncology* 2003;13(3):189-202.

72. Cheung WY, Garratt AM, Russell IT, Williams JG. The UK IBDQ-a British version of the inflammatory bowel disease questionnaire. development and validation. *Journal of clinical epidemiology* 2000;53(3):297-306.

73. Olopade FA, Norman A, Blake P, Dearnaley DP, Harrington KJ, Khoo V, et al. A modified Inflammatory Bowel Disease questionnaire and the Vaizey Incontinence questionnaire are simple ways to identify patients with significant gastrointestinal symptoms after pelvic radiotherapy. *Br J Cancer* 2005;92(9):1663-70.

74. McGough C, Wedlake L, Baldwin C, Hackett C, Norman AR, Blake P, et al. Clinical trial: normal diet vs. partial replacement with oral E028 formula for the prevention of gastrointestinal toxicity in cancer patients undergoing pelvic radiotherapy. *Aliment Pharmacol Ther* 2008;27(11):1132-9.

75. McNair HA, Wedlake L, McVey GP, Thomas K, Andreyev J, Dearnaley DP. Can diet combined with treatment scheduling achieve consistency of rectal filling in patients receiving radiotherapy to the prostate? *Radiother Oncol* 2011;101(3):471-8.

76. Wedlake LJ, McGough C, Shaw C, Klopper T, Thomas K, Lalji A, et al. Clinical trial: Efficacy of a low or modified fat diet for the prevention of gastrointestinal toxicity in patients receiving radiotherapy treatment for pelvic malignancies. *J Hum Nutr Diet* 2012;25(3):247-59.

77. Abraham C, Cho JH. Inflammatory bowel disease. *The New England journal of medicine* 2009;361(21):2066-78.

78. Hauer-Jensen M, Wang J, Boerma M, Fu Q, Denham JW. Radiation damage to the gastrointestinal tract: mechanisms, diagnosis, and management. *Current opinion in supportive and palliative care* 2007;1(1):23-9.

79. MacNaughton WK. Review article: new insights into the pathogenesis of radiation-induced intestinal dysfunction. *Aliment Pharmacol Ther* 2000;14(5):523-8.

80. Kaser A, Zeissig S, Blumberg RS. Inflammatory bowel disease. *Annual review of immunology* 2010;28:573-621.

81. Cabre E, Manosa M, Garcia-Sanchez V, Gutierrez A, Ricart E, Esteve M, et al. Phenotypic concordance in familial inflammatory bowel disease (IBD). Results of a nationwide IBD Spanish database. *Journal of Crohn's & colitis* 2013.

82. Karban A, Eliakim R, Brant SR. Genetics of inflammatory bowel disease. *The Israel Medical Association journal : IMAJ* 2002;4(10):798-802.

83. Hendrickson BA, Gokhale R, Cho JH. Clinical aspects and pathophysiology of inflammatory bowel disease. *Clinical microbiology reviews* 2002;15(1):79-94.

84. Ferreira MR, Muls A, Dearnaley DP, Andreyev HJ. Microbiota and radiation-induced bowel toxicity: lessons from inflammatory bowel disease for the radiation oncologist. *Lancet Oncol* 2014;15(3):e139-47.

85. Gersemann M, Wehkamp J, Stange EF. Innate immune dysfunction in inflammatory bowel disease. *Journal of internal medicine* 2012;271(5):421-8.

86. Gerasimidis K, McGrogan P, Edwards CA. The aetiology and impact of malnutrition in paediatric inflammatory bowel disease. *J Hum Nutr Diet* 2011;24(4):313-26.

87. Barnett GC, Coles CE, Elliott RM, Baynes C, Luccarini C, Conroy D, et al. Independent validation of genes and polymorphisms reported to be associated with radiation toxicity: a prospective analysis study. *Lancet Oncol* 2012;13(1):65-77.

88. Nguyen NP, Antoine JE, Dutta S, Karlsson U, Sallah S. Current concepts in radiation enteritis and implications for future clinical trials. *Cancer* 2002;95(5):1151-63.

89. Francois A, Milliat F, Guipaud O, Benderitter M. Inflammation and immunity in radiation damage to the gut mucosa. *BioMed research international* 2013;2013:123241.

90. Somosy Z, Horvath G, Telbisz A, Rez G, Palfia Z. Morphological aspects of ionizing radiation response of small intestine. *Micron (Oxford, England : 1993)* 2002;33(2):167-78.

91. Yeoh AS, Gibson RJ, Yeoh EE, Bowen JM, Stringer AM, Giam KA, et al. A novel animal model to investigate fractionated radiotherapy-induced alimentary mucositis: the role of apoptosis, p53, nuclear factor-kappaB, COX-1, and COX-2. *Molecular cancer therapeutics* 2007;6(8):2319-27.

92. Nejdfors P, Ekelund M, Westrom BR, Willen R, Jeppsson B. Intestinal permeability in humans is increased after radiation therapy. *Diseases of the colon and rectum* 2000;43(11):1582-87; discussion 87-8.

93. Yeoh AS, Bowen JM, Gibson RJ, Keefe DM. Nuclear factor kappaB (NFkappaB) and cyclooxygenase-2 (Cox-2) expression in the irradiated colorectum is associated with

subsequent histopathological changes. *Int J Radiat Oncol Biol Phys* 2005;63(5):1295-303.

94. Abraham C, Medzhitov R. Interactions between the host innate immune system and microbes in inflammatory bowel disease. *Gastroenterology* 2011;140(6):1729-37.

95. Schaue D, McBride WH. Links between innate immunity and normal tissue radiobiology. *Radiation research* 2010;173(4):406-17.

96. Linard C, Ropenga A, Vozenin-Brotons MC, Chapel A, Mathe D. Abdominal irradiation increases inflammatory cytokine expression and activates NF-kappaB in rat ileal muscularis layer. *American journal of physiology. Gastrointestinal and liver physiology* 2003;285(3):G556-65.

97. Shan YX, Jin SZ, Liu XD, Liu Y, Liu SZ. Ionizing radiation stimulates secretion of pro-inflammatory cytokines: dose-response relationship, mechanisms and implications. *Radiation and environmental biophysics* 2007;46(1):21-9.

98. Wang J, Boerma M, Fu Q, Hauer-Jensen M. Significance of endothelial dysfunction in the pathogenesis of early and delayed radiation enteropathy. *World journal of gastroenterology : WJG* 2007;13(22):3047-55.

99. Molla M, Panes J. Radiation-induced intestinal inflammation. *World journal of gastroenterology : WJG* 2007;13(22):3043-6.

100. Mihaescu A, Thornberg C, Mattsson S, Wang Y, Jeppsson B, Thorlacius H. Critical role of P-selectin and lymphocyte function antigen-1 in radiation-induced leukocyte-endothelial cell interactions in the colon. *Diseases of the colon and rectum* 2007;50(12):2194-202.

101. Ikeda Y, Ito M, Matsuu M, Shichijo K, Fukuda E, Nakayama T, et al. Expression of ICAM-1 and acute inflammatory cell infiltration in the early phase of radiation colitis in rats. *Journal of radiation research* 2000;41(3):279-91.

102. Mihaescu A, Santen S, Jeppsson B, Thorlacius H. Rho kinase signalling mediates radiation-induced inflammation and intestinal barrier dysfunction. *The British journal of surgery* 2011;98(1):124-31.

103. Mihaescu A, Santen S, Jeppsson B, Thorlacius H. p38 Mitogen-activated protein kinase signalling regulates vascular inflammation and epithelial barrier dysfunction in an experimental model of radiation-induced colitis. *The British journal of surgery* 2010;97(2):226-34.

104. Dent P, Yacoub A, Fisher PB, Hagan MP, Grant S. MAPK pathways in radiation responses. *Oncogene* 2003;22(37):5885-96.

105. Kumar S, Boehm J, Lee JC. p38 MAP kinases: key signalling molecules as therapeutic targets for inflammatory diseases. *Nature reviews. Drug discovery* 2003;2(9):717-26.

106. Cole AT, Slater K, Sokal M, Hawkey CJ. In vivo rectal inflammatory mediator changes with radiotherapy to the pelvis. *Gut* 1993;34(9):1210-4.

107. Ong ZY, Gibson RJ, Bowen JM, Stringer AM, Darby JM, Logan RM, et al. Pro-inflammatory cytokines play a key role in the development of radiotherapy-induced gastrointestinal mucositis. *Radiation oncology (London, England)* 2010;5:22.

108. Christensen E, Pintilie M, Evans KR, Lenarduzzi M, Menard C, Catton CN, et al. Longitudinal cytokine expression during IMRT for prostate cancer and acute treatment toxicity. *Clinical cancer research : an official journal of the American Association for Cancer Research* 2009;15(17):5576-83.

109. Lopes CO, Callera F. Three-dimensional conformal radiotherapy in prostate cancer patients: rise in interleukin 6 (IL-6) but not IL-2, IL-4, IL-5, tumor necrosis factor-alpha, MIP-1-alpha, and LIF levels. *Int J Radiat Oncol Biol Phys* 2012;82(4):1385-8.

110. Manichanh C, Borruel N, Casellas F, Guarner F. The gut microbiota in IBD. *Nature reviews. Gastroenterology & hepatology* 2012;9(10):599-608.

111. Neish AS. Microbes in gastrointestinal health and disease. *Gastroenterology* 2009;136(1):65-80.

112. Parfrey LW, Knight R. Spatial and temporal variability of the human microbiota. *Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases* 2012;18 Suppl 4:8-11.

113. Chassard C, Lacroix C. Carbohydrates and the human gut microbiota. *Current opinion in clinical nutrition and metabolic care* 2013;16(4):453-60.

114. Machiels K, Joossens M, Sabino J, De Preter V, Arijs I, Eeckhaut V, et al. A decrease of the butyrate-producing species Roseburia hominis and Faecalibacterium prausnitzii defines dysbiosis in patients with ulcerative colitis. *Gut* 2013.

115. Wang W, Chen L, Zhou R, Wang X, Song L, Huang S, et al. Increased proportions of Bifidobacterium and the Lactobacillus group and loss of butyrate-producing bacteria in inflammatory bowel disease. *Journal of clinical microbiology* 2014;52(2):398-406.

116. Morgan XC, Tickle TL, Sokol H, Gevers D, Devaney KL, Ward DV, et al. Dysfunction of the intestinal microbiome in inflammatory bowel disease and treatment. *Genome biology* 2012;13(9):R79.

117. Korshunov VM, Ikonnikova TB, Kissina EV, Tarabrina NP, Pinegin BV. [Microflora study of the intestinal cavity and mucosa normally and after gamma irradiation]. *Zhurnal mikrobiologii, epidemiologii, i immunobiologii* 1980(9):65-70.

118. Arasaradnam RP, Quraishi N, Kyrou I, Nwokolo CU, Joseph M, Kumar S, et al. Insights into 'fermentonomics': evaluation of volatile organic compounds (VOCs) in human disease using an electronic 'e-nose'. *Journal of medical engineering & technology* 2011;35(2):87-91.

119. Husebye E, Skar V, Hoverstad T, Iversen T, Melby K. Abnormal intestinal motor patterns explain enteric colonization with gram-negative bacilli in late radiation enteropathy. *Gastroenterology* 1995;109(4):1078-89.

120. Ciorba MA, Stenson WF. Probiotic therapy in radiation-induced intestinal injury and repair. *Annals of the New York Academy of Sciences* 2009;1165:190-4.

121. Crawford PA, Gordon JI. Microbial regulation of intestinal radiosensitivity. *Proceedings of the National Academy of Sciences of the United States of America* 2005;102(37):13254-9.

122. Ciorba MA, Riehl TE, Rao MS, Moon C, Ee X, Nava GM, et al. Lactobacillus probiotic protects intestinal epithelium from radiation injury in a TLR-2/cyclo-oxygenase-2-dependent manner. *Gut* 2012;61(6):829-38.

123. Riehl T, Cohn S, Tessner T, Schloemann S, Stenson WF. Lipopolysaccharide is radioprotective in the mouse intestine through a prostaglandin-mediated mechanism. *Gastroenterology* 2000;118(6):1106-16.

124. Riehl TE, Newberry RD, Lorenz RG, Stenson WF. TNFR1 mediates the radioprotective effects of lipopolysaccharide in the mouse intestine. *American journal of physiology. Gastrointestinal and liver physiology* 2004;286(1):G166-73.

125. Gibson RJ, Keefe DM, Lalla RV, Bateman E, Blijlevens N, Fijlstra M, et al. Systematic review of agents for the management of gastrointestinal mucositis in cancer patients. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer* 2013;21(1):313-26.

126. Oates RW, McPhee NJ, Joon ML, Schneider-Kolsky M, Kron T. Recording a patient diary over the radical course of radiotherapy for prostate cancer using a diet diary: A feasibility study. *J Radiother Pract* 2013;12:18-25.

127. Wedlake LJ, Shaw C, Whelan K, Andreyev HJ. Systematic review: the efficacy of nutritional interventions to counteract acute gastrointestinal toxicity during therapeutic pelvic radiotherapy. *Aliment Pharmacol Ther* 2013;37(11):1046-56.

128. McGough C, Baldwin C, Frost G, Andreyev HJ. Role of nutritional intervention in patients treated with radiotherapy for pelvic malignancy. *Br J Cancer* 2004;90(12):2278-87.

129. Henson CC, Burden S, Davidson SE, Lal S. Nutritional interventions for reducing gastrointestinal toxicity in adults undergoing radical pelvic radiotherapy. *The Cochrane database of systematic reviews* 2013;11:CD009896.

130. Murphy J, Stacey D, Crook J, Thompson B, Panetta D. Testing control of radiation-induced diarrhea with a psyllium bulking agent: a pilot study. *Canadian oncology nursing journal = Revue canadienne de nursing oncologique* 2000;10(3):96-100.

131. Fuccio L, Guido A, Eusebi LH, Laterza L, Grilli D, Cennamo V, et al. Effects of probiotics for the prevention and treatment of radiation-induced diarrhea. *Journal of clinical gastroenterology* 2009;43(6):506-13.

132. Hamad A, Fragkos KC, Forbes A. A systematic review and meta-analysis of probiotics for the management of radiation induced bowel disease. *Clinical nutrition (Edinburgh, Scotland)* 2013;32(3):353-60.

133. Cook SI, Sellin JH. Review article: short chain fatty acids in health and disease. *Aliment Pharmacol Ther* 1998;12(6):499-507.

134. Englyst HN, Trowell H, Southgate DA, Cummings JH. Dietary fiber and resistant starch. *Am J Clin Nutr* 1987;46(6):873-4.

135. McCleary BV. Dietary fibre analysis. *The Proceedings of the Nutrition Society* 2003;62(1):3-9.

136. Medicine FaNBotIo. *Dietary Reference Intakes Proposed Definition of Dietary Fiber*. Washington: National Academy Press, 2001.

137. Cummings JH, Mann JI, Nishida C, Vorster HH. Dietary fibre: an agreed definition. *Lancet* 2009;373(9661):365-6.

138. Mann JI, Cummings JH. Possible implications for health of the different definitions of dietary fibre. *Nutrition, metabolism, and cardiovascular diseases : NMCD* 2009;19(3):226-9.

139. COMA. Non-starch Polysaccharides *Report on Health and Social Subjects no. 41. Dietary Reference Values for Food, Energy and Nutrients for the United Kingdom. Report of the Panel on Dietary Reference Values of the Committee on Medical Aspects of Food Policy.* . London: HMSO, 1991:61-71.

140. Bender DE, Bender AE. Carbohyhdrates. *Nutrition a reference handbook*. Oxford: Oxford University Press, 1997:109 - 21.

141. Staudacher HM, Irving PM, Lomer MC, Whelan K. Mechanisms and efficacy of dietary FODMAP restriction in IBS. *Nature reviews. Gastroenterology & hepatology* 2014;11(4):256-66.

142. Roberfroid M, Gibson GR, Hoyles L, McCartney AL, Rastall R, Rowland I, et al. Prebiotic effects: metabolic and health benefits. *The British journal of nutrition* 2010;104 Suppl 2:S1-63.

143. Slavin JL. Position of the American Dietetic Association: health implications of dietary fiber. *Journal of the American Dietetic Association* 2008;108(10):1716-31.

144. US Department of Agriculture, Services UDoHaH. Dietary Guidelines for Americans. US, 2010.

145. Federation FaD. The Facts: Science behind Guideline Daily Amounts. In: Saunders T, editor. www.fdf.org.uk, 2012.

146. Goldsmith JR, Sartor RB. The role of diet on intestinal microbiota metabolism: downstream impacts on host immune function and health, and therapeutic implications. *Journal of gastroenterology* 2014;49(5):785-98.

147. Ursell LK, Haiser HJ, Van Treuren W, Garg N, Reddivari L, Vanamala J, et al. The Intestinal Metabolome: An Intersection Between Microbiota and Host. *Gastroenterology* 2014.

148. Larsbrink J, Rogers TE, Hemsworth GR, McKee LS, Tauzin AS, Spadiut O, et al. A discrete genetic locus confers xyloglucan metabolism in select human gut Bacteroidetes. *Nature* 2014;506(7489):498-502.

149. Wu GD, Chen J, Hoffmann C, Bittinger K, Chen YY, Keilbaugh SA, et al. Linking long-term dietary patterns with gut microbial enterotypes. *Science (New York, N.Y.)* 2011;334(6052):105-8.

150. David LA, Maurice CF, Carmody RN, Gootenberg DB, Button JE, Wolfe BE, et al. Diet rapidly and reproducibly alters the human gut microbiome. *Nature* 2014;505(7484):559-63.

151. Zimmer J, Lange B, Frick JS, Sauer H, Zimmermann K, Schwiertz A, et al. A vegan or vegetarian diet substantially alters the human colonic faecal microbiota. *European journal of clinical nutrition* 2012;66(1):53-60.

152. Claesson MJ, Jeffery IB, Conde S, Power SE, O'Connor EM, Cusack S, et al. Gut microbiota composition correlates with diet and health in the elderly. *Nature* 2012;488(7410):178-84.

153. Macfarlane S, Macfarlane GT. Regulation of short-chain fatty acid production. *The Proceedings of the Nutrition Society* 2003;62(1):67-72.

154. Ganapathy V, Thangaraju M, Prasad PD, Martin PM, Singh N. Transporters and receptors for short-chain fatty acids as the molecular link between colonic bacteria and the host. *Current opinion in pharmacology* 2013;13(6):869-74.

155. Cuervo A, Salazar N, Ruas-Madiedo P, Gueimonde M, Gonzalez S. Fiber from a regular diet is directly associated with fecal short-chain fatty acid concentrations in the elderly. *Nutrition research (New York, N.Y.)* 2013;33(10):811-6.

156. McOrist AL, Miller RB, Bird AR, Keogh JB, Noakes M, Topping DL, et al. Fecal butyrate levels vary widely among individuals but are usually increased by a diet high in resistant starch. *The Journal of nutrition* 2011;141(5):883-9.

157. Whelan K, Judd PA, Preedy VR, Simmering R, Jann A, Taylor MA. Fructooligosaccharides and fiber partially prevent the alterations in fecal microbiota and short-chain fatty acid concentrations caused by standard enteral formula in healthy humans. *The Journal of nutrition* 2005;135(8):1896-902.

158. Benus RF, van der Werf TS, Welling GW, Judd PA, Taylor MA, Harmsen HJ, et al. Association between Faecalibacterium prausnitzii and dietary fibre in colonic fermentation in healthy human subjects. *The British journal of nutrition* 2010;104(5):693-700.

159. Andreyev HJN. Chronic proctitis versus chronic protopathy: Personal Communication, London 2014.

160. Talley NA, Chen F, King D, Jones M, Talley NJ. Short-chain fatty acids in the treatment of radiation proctitis: a randomized, double-blind, placebo-controlled, cross-over pilot trial. *Diseases of the colon and rectum* 1997;40(9):1046-50.

161. Pinto A, Fidalgo P, Cravo M, Midoes J, Chaves P, Rosa J, et al. Short chain fatty acids are effective in short-term treatment of chronic radiation proctitis: randomized, double-blind, controlled trial. *Diseases of the colon and rectum* 1999;42(6):788-95; discussion 95-6.

162. Vernia P, Fracasso PL, Casale V, Villotti G, Marcheggiano A, Stigliano V, et al. Topical butyrate for acute radiation proctitis: randomised, crossover trial. *Lancet* 2000;356(9237):1232-5.

163. al-Sabbagh R, Sinicrope FA, Sellin JH, Shen Y, Roubein L. Evaluation of short-chain fatty acid enemas: treatment of radiation proctitis. *The American journal of gastroenterology* 1996;91(9):1814-6.

164. Hille A, Herrmann MK, Kertesz T, Christiansen H, Hermann RM, Pradier O, et al. Sodium butyrate enemas in the treatment of acute radiation-induced proctitis in

patients with prostate cancer and the impact on late proctitis. A prospective evaluation. *Strahlentherapie und Onkologie : Organ der Deutschen Rontgengesellschaft ... [et al]* 2008;184(12):686-92.

165. Breuer RI, Buto SK, Christ ML, Bean J, Vernia P, Paoluzi P, et al. Rectal irrigation with short-chain fatty acids for distal ulcerative colitis. Preliminary report. *Digestive diseases and sciences* 1991;36(2):185-7.

166. Scheppach W, Sommer H, Kirchner T, Paganelli GM, Bartram P, Christl S, et al. Effect of butyrate enemas on the colonic mucosa in distal ulcerative colitis. *Gastroenterology* 1992;103(1):51-6.

167. Vernia P, Cittadini M, Caprilli R, Torsoli A. Topical treatment of refractory distal ulcerative colitis with 5-ASA and sodium butyrate. *Digestive diseases and sciences* 1995;40(2):305-7.

168. Patz J, Jacobsohn WZ, Gottschalk-Sabag S, Zeides S, Braverman DZ. Treatment of refractory distal ulcerative colitis with short chain fatty acid enemas. *The American journal of gastroenterology* 1996;91(4):731-4.

169. Vernia P, Marcheggiano A, Caprilli R, Frieri G, Corrao G, Valpiani D, et al. Short-chain fatty acid topical treatment in distal ulcerative colitis. *Aliment Pharmacol Ther* 1995;9(3):309-13.

170. Vernia P, Annese V, Bresci G, d'Albasio G, D'Inca R, Giaccari S, et al. Topical butyrate improves efficacy of 5-ASA in refractory distal ulcerative colitis: results of a multicentre trial. *European journal of clinical investigation* 2003;33(3):244-8.

171. Steinhart AH, Hiruki T, Brzezinski A, Baker JP. Treatment of left-sided ulcerative colitis with butyrate enemas: a controlled trial. *Aliment Pharmacol Ther* 1996;10(5):729-36.

172. Breuer RI, Soergel KH, Lashner BA, Christ ML, Hanauer SB, Vanagunas A, et al. Short chain fatty acid rectal irrigation for left-sided ulcerative colitis: a randomised, placebo controlled trial. *Gut* 1997;40(4):485-91.

173. Hamer HM, Jonkers DM, Vanhoutvin SA, Troost FJ, Rijkers G, de Bruine A, et al. Effect of butyrate enemas on inflammation and antioxidant status in the colonic mucosa of patients with ulcerative colitis in remission. *Clinical nutrition (Edinburgh, Scotland)* 2010;29(6):738-44.

174. Vinolo MA, Rodrigues HG, Nachbar RT, Curi R. Regulation of inflammation by short chain fatty acids. *Nutrients* 2011;3(10):858-76.

175. Liu T, Li J, Liu Y, Xiao N, Suo H, Xie K, et al. Short-chain fatty acids suppress lipopolysaccharide-induced production of nitric oxide and proinflammatory

cytokines through inhibition of NF-kappaB pathway in RAW264.7 cells. *Inflammation* 2012;35(5):1676-84.

176. Segain JP, Raingeard de la Bletiere D, Bourreille A, Leray V, Gervois N, Rosales C, et al. Butyrate inhibits inflammatory responses through NFkappaB inhibition: implications for Crohn's disease. *Gut* 2000;47(3):397-403.

177. Tedelind S, Westberg F, Kjerrulf M, Vidal A. Anti-inflammatory properties of the short-chain fatty acids acetate and propionate: a study with relevance to inflammatory bowel disease. *World journal of gastroenterology : WJG* 2007;13(20):2826-32.

178. Furusawa Y, Obata Y, Fukuda S, Endo TA, Nakato G, Takahashi D, et al. Commensal microbe-derived butyrate induces the differentiation of colonic regulatory T cells. *Nature* 2013;504(7480):446-50.

179. Arpaia N, Campbell C, Fan X, Dikiy S, van der Veeken J, deRoos P, et al. Metabolites produced by commensal bacteria promote peripheral regulatory T-cell generation. *Nature* 2013;504(7480):451-5.

180. Russo I, Luciani A, De Cicco P, Troncone E, Ciacci C. Butyrate attenuates lipopolysaccharide-induced inflammation in intestinal cells and Crohn's mucosa through modulation of antioxidant defense machinery. *PloS one* 2012;7(3):e32841.

181. Maslowski KM, Vieira AT, Ng A, Kranich J, Sierro F, Yu D, et al. Regulation of inflammatory responses by gut microbiota and chemoattractant receptor GPR43. *Nature* 2009;461(7268):1282-6.

182. Binder HJ. Role of colonic short-chain fatty acid transport in diarrhea. *Annual review of physiology* 2010;72:297-313.

183. Kunzelmann K, Mall M. Electrolyte transport in the mammalian colon: mechanisms and implications for disease. *Physiological reviews* 2002;82(1):245-89.

184. Manokas T, Fromkes JJ, Sundaram U. Effect of chronic inflammation on ileal short-chain fatty acid/bicarbonate exchange. *American journal of physiology. Gastrointestinal and liver physiology* 2000;278(4):G585-90.

185. Rabbani GH, Albert MJ, Rahman H, Chowdhury AK. Short-chain fatty acids inhibit fluid and electrolyte loss induced by cholera toxin in proximal colon of rabbit in vivo. *Digestive diseases and sciences* 1999;44(8):1547-53.

186. Hamer HM, Jonkers D, Venema K, Vanhoutvin S, Troost FJ, Brummer RJ. Review article: the role of butyrate on colonic function. *Aliment Pharmacol Ther* 2008;27(2):104-19.

187. Peng L, Li ZR, Green RS, Holzman IR, Lin J. Butyrate enhances the intestinal barrier by facilitating tight junction assembly via activation of AMP-activated protein kinase in Caco-2 cell monolayers. *The Journal of nutrition* 2009;139(9):1619-25.

188. Ploger S, Stumpff F, Penner GB, Schulzke JD, Gabel G, Martens H, et al. Microbial butyrate and its role for barrier function in the gastrointestinal tract. *Annals of the New York Academy of Sciences* 2012;1258:52-9.

189. Lewis K, Lutgendorff F, Phan V, Soderholm JD, Sherman PM, McKay DM. Enhanced translocation of bacteria across metabolically stressed epithelia is reduced by butyrate. *Inflammatory bowel diseases* 2010;16(7):1138-48.

190. Higgins JPT, Green S. *Cochrane Handbook for Systematic Reviews of Interventions.* Chichester, UK: John Wiley & Sons, 2008.

191. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Ann Intern Med* 2009;151(4):W65-94.

192. Moher D, Tricco AC. Issues related to the conduct of systematic reviews: a focus on the nutrition field. *Am J Clin Nutr* 2008;88(5):1191-9.

193. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Controlled clinical trials* 1996;17(1):1-12.

194. Fernandez-Banares F, Hinojosa J, Sanchez-Lombrana JL, Navarro E, Martinez-Salmeron JF, Garcia-Puges A, et al. Randomized clinical trial of Plantago ovata seeds (dietary fiber) as compared with mesalamine in maintaining remission in ulcerative colitis. Spanish Group for the Study of Crohn's Disease and Ulcerative Colitis (GETECCU). *The American journal of gastroenterology* 1999;94(2):427-33.

195. Hallert C, Kaldma M, Petersson BG. Ispaghula husk may relieve gastrointestinal symptoms in ulcerative colitis in remission. *Scandinavian journal of gastroenterology* 1991;26(7):747-50.

196. Copachi IC, Rovinarul et al. Maintenance of remission of ulcerative colitis (UC): Mesalamine, dietary fiber, S. boulardi. *Digestive diseases and sciences* 2000;32(Supplement 1):A2.

197. Faghfoori Z, Navai L, Shakerhosseini R, Somi MH, Nikniaz Z, Norouzi MF. Effects of an oral supplementation of germinated barley foodstuff on serum tumour necrosis factor-alpha, interleukin-6 and -8 in patients with ulcerative colitis. *Annals of clinical biochemistry* 2011;48(Pt 3):233-7.

198. Federico A, Tuccillo C, Grossi E, Abbiati R, Garbagna N, Romano M, et al. The effect of a new symbiotic formulation on plasma levels and peripheral blood mononuclear cell expression of some pro-inflammatory cytokines in patients with ulcerative colitis: a pilot study. *European review for medical and pharmacological sciences* 2009;13(4):285-93.

199. Furrie E, Macfarlane S, Kennedy A, Cummings JH, Walsh SV, O'Neil D A, et al. Synbiotic therapy (Bifidobacterium longum/Synergy 1) initiates resolution of inflammation in patients with active ulcerative colitis: a randomised controlled pilot trial. *Gut* 2005;54(2):242-9.

200. Casellas F, Borruel N, Torrejon A, Varela E, Antolin M, Guarner F, et al. Oral oligofructose-enriched inulin supplementation in acute ulcerative colitis is well tolerated and associated with lowered faecal calprotectin. *Aliment Pharmacol Ther* 2007;25(9):1061-7.

201. Kanauchi O, Suga T, Tochihara M, Hibi T, Naganuma M, Homma T, et al. Treatment of ulcerative colitis by feeding with germinated barley foodstuff: first report of a multicenter open control trial. *Journal of gastroenterology* 2002;37 Suppl 14:67-72.

202. Ishikawa H, Matsumoto S, Ohashi Y, Imaoka A, Setoyama H, Umesaki Y, et al. Beneficial effects of probiotic bifidobacterium and galacto-oligosaccharide in patients with ulcerative colitis: a randomized controlled study. *Digestion* 2011;84(2):128-33.

203. Fujimori S, Gudis K, Mitsui K, Seo T, Yonezawa M, Tanaka S, et al. A randomized controlled trial on the efficacy of synbiotic versus probiotic or prebiotic treatment to improve the quality of life in patients with ulcerative colitis. *Nutrition (Burbank, Los Angeles County, Calif.)* 2009;25(5):520-5.

204. Chermesh I, Tamir A, Reshef R, Chowers Y, Suissa A, Katz D, et al. Failure of Synbiotic 2000 to prevent postoperative recurrence of Crohn's disease. *Digestive diseases and sciences* 2007;52(2):385-9.

205. Rutgeerts P DHG, Baert F, et al. Randomised placebo controlled trial of pro- and prebiotics (synbiotics cocktail) for the maintenance of infliximab induced remission of luminal Crohn's disease (CD). . *Gastroenterology* 2004;126(4):A467.

206. Jones VA, Dickinson RJ, Workman E, Wilson AJ, Freeman AH, Hunter JO. Crohn's disease: maintenance of remission by diet. *Lancet* 1985;2(8448):177-80.

207. Ritchie JK, Wadsworth J, Lennard-Jones JE, Rogers E. Controlled multicentre therapeutic trial of an unrefined carbohydrate, fibre rich diet in Crohn's disease. *British medical journal (Clinical research ed.)* 1987;295(6597):517-20.

208. Steed H, Macfarlane GT, Blackett KL, Bahrami B, Reynolds N, Walsh SV, et al. Clinical trial: the microbiological and immunological effects of synbiotic consumption - a randomized double-blind placebo-controlled study in active Crohn's disease. *Aliment Pharmacol Ther* 2010;32(7):872-83.

209. Benjamin JL, Hedin CR, Koutsoumpas A, Ng SC, McCarthy NE, Hart AL, et al. Randomised, double-blind, placebo-controlled trial of fructo-oligosaccharides in active Crohn's disease. *Gut* 2011;60(7):923-9.

210. Koch H. Adjuvant treatment of Crohn's disease with a psyllium preparation. [Article in German]. *Therapiewoche* 1984;34:4545-48.

211. Bartel G, Weiss I, Turetschek K, Schima W, Puspok A, Waldhoer T, et al. Ingested matter affects intestinal lesions in Crohn's disease. *Inflammatory bowel diseases* 2008;14(3):374-82.

212. Brotherton CS TA, Anderson GJ. Can a high fiber diet improve bowel function and helath-related quality of life in patients with Crohn's disease? *FASEB Journal* 2012;AN: 70854169.

213. Joossens M, De Preter V, Ballet V, Verbeke K, Rutgeerts P, Vermeire S. Effect of oligofructose-enriched inulin (OF-IN) on bacterial composition and disease activity of patients with Crohn's disease: results from a double-blinded randomised controlled trial. *Gut* 2012;61(6):958.

214. Levenstein S, Prantera C, Luzi C, D'Ubaldi A. Low residue or normal diet in Crohn's disease: a prospective controlled study in Italian patients. *Gut* 1985;26(10):989-93.

215. Stange EF SU, Fleig WE et al. Exclusion diet in Crohn's disease: A controlled, randomised study. [Article in German]. *Z Gastroenterol* 1990;28:561-64.

216. Welters CF, Heineman E, Thunnissen FB, van den Bogaard AE, Soeters PB, Baeten CG. Effect of dietary inulin supplementation on inflammation of pouch mucosa in patients with an ileal pouch-anal anastomosis. *Diseases of the colon and rectum* 2002;45(5):621-7.

217. Sears CL. Enterotoxigenic Bacteroides fragilis: a rogue among symbiotes. *Clinical microbiology reviews* 2009;22(2):349-69, Table of Contents.

218. Freeman HJ. Application of the Montreal classification for Crohn's disease to a single clinician database of 1015 patients. *Canadian journal of gastroenterology = Journal canadien de gastroenterologie* 2007;21(6):363-6.

219. Wedlake L, Slack N, Andreyev HJ, Whelan K. Fiber in the Treatment and Maintenance of Inflammatory Bowel Disease: A Systematic Review of Randomized Controlled Trials. *Inflammatory bowel diseases* 2014.

220. Lodge N, Evans ML, Wilkins M, Blake PR, Fryatt I. A randomized cross-over study of the efficacy of codeine phosphate versus Ispaghulahusk in patients with gynaecological cancer experiencing diarrhoea during pelvic radiotherapy. *European journal of cancer care* 1995;4(1):8-10.

221. Salminen E, Elomaa I, Minkkinen J, Vapaatalo H, Salminen S. Preservation of intestinal integrity during radiotherapy using live Lactobacillus acidophilus cultures. *Clinical radiology* 1988;39(4):435-7.

222. Pettersson A, Johansson B, Persson C, Berglund A, Turesson I. Effects of a dietary intervention on acute gastrointestinal side effects and other aspects of health-related quality of life: a randomized controlled trial in prostate cancer patients undergoing radiotherapy. *Radiother Oncol* 2012;103(3):333-40.

223. Garcia-Peris P, Velasco C, Lozano MA, Moreno Y, Paron L, de la Cuerda C, et al. Effect of a mixture of inulin and fructo-oligosaccharide on Lactobacillus and Bifidobacterium intestinal microbiota of patients receiving radiotherapy: a randomised, double-blind, placebo-controlled trial. *Nutricion hospitalaria* 2012;27(6):1908-15.

224. Macmillan Cancer Support DoH, NHS England. National Cancer Survisorship Initiative. www.ncsi.org.uk, 2013.

225. Eswaran S, Muir J, Chey WD. Fiber and functional gastrointestinal disorders. *The American journal of gastroenterology* 2013;108(5):718-27.

226. Englyst HN, ME Q, GJ H, JH C. Determination of dietary fibre as non-starch polysaccharides by gas-liquid chromatography. *Analyst* 1992;117:1707-04.

227. Henderson L GJ, Irving K, Swan G. *The National Diet and Nutrition Survey: adults aged 19 - 64 years. Volume 2: Energy, protein, carbohydrate, fat and alcohol intake*. London: TSO (The Stationery Office), 2003.

228. Armitage HE MC, Wedlake LJ, Whelan K, Andreyev HJN. The impact of radical pelvic radiotherapy on nutrient intake. *BAPEN Abstracts* 2007.

229. Chlebowski RT, Blackburn GL, Buzzard IM, Rose DP, Martino S, Khandekar JD, et al. Adherence to a dietary fat intake reduction program in postmenopausal women receiving therapy for early breast cancer. The Women's Intervention Nutrition Study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 1993;11(11):2072-80.

230. Chlebowski RT, Blackburn GL, Thomson CA, Nixon DW, Shapiro A, Hoy MK, et al. Dietary fat reduction and breast cancer outcome: interim efficacy results from the Women's Intervention Nutrition Study. *Journal of the National Cancer Institute* 2006;98(24):1767-76.

231. Chlebowski RT, Nixon DW, Blackburn GL, Jochimsen P, Scanlon EF, Insull W, Jr., et al. A breast cancer Nutrition Adjuvant Study (NAS): protocol design and initial patient adherence. *Breast cancer research and treatment* 1987;10(1):21-9.

232. Bacon CG, Giovannucci E, Testa M, Glass TA, Kawachi I. The association of treatment-related symptoms with quality-of-life outcomes for localized prostate carcinoma patients. *Cancer* 2002;94(3):862-71.

233. Guyatt G, Mitchell A, Irvine EJ, Singer J, Williams N, Goodacre R, et al. A new measure of health status for clinical trials in inflammatory bowel disease. *Gastroenterology* 1989;96(3):804-10.

234. Hlavaty T, Persoons P, Vermeire S, Ferrante M, Pierik M, Van Assche G, et al. Evaluation of short-term responsiveness and cutoff values of inflammatory bowel disease questionnaire in Crohn's disease. *Inflammatory bowel diseases* 2006;12(3):199-204.

235. Higgins PD, Schwartz M, Mapili J, Krokos I, Leung J, Zimmermann EM. Patient defined dichotomous end points for remission and clinical improvement in ulcerative colitis. *Gut* 2005;54(6):782-8.

236. NIHR. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Good Clinical Practice (ICH GCP) 1996. www.crncc.nihr, 2013.

237. Altman DG, Schulz KF, Moher D, Egger M, Davidoff F, Elbourne D, et al. The revised CONSORT statement for reporting randomized trials: explanation and elaboration. *Ann Intern Med* 2001;134(8):663-94.

238. Bingham SA, Gill C, Welch A, Day K, Cassidy A, Khaw KT, et al. Comparison of dietary assessment methods in nutritional epidemiology: weighed records v. 24 h recalls, food-frequency questionnaires and estimated-diet records. *The British journal of nutrition* 1994;72(4):619-43.

239. Agency FS. *Food Portion Sizes*. Third Edition ed. London: TSO London, 1988.

240. Heaton KW, Ghosh S, Braddon FE. How bad are the symptoms and bowel dysfunction of patients with the irritable bowel syndrome? A prospective, controlled study with emphasis on stool form. *Gut* 1991;32(1):73-9.

241. Hallert C, Bjorck I, Nyman M, Pousette A, Granno C, Svensson H. Increasing fecal butyrate in ulcerative colitis patients by diet: controlled pilot study. *Inflammatory bowel diseases* 2003;9(2):116-21.

242. Vaizey CJ, Carapeti E, Cahill JA, Kamm MA. Prospective comparison of faecal incontinence grading systems. *Gut* 1999;44(1):77-80.

243. Whelan K, Judd PA, Preedy VR, Taylor MA. Covert assessment of concurrent and construct validity of a chart to characterize fecal output and diarrhea in patients receiving enteral nutrition. *JPEN. Journal of parenteral and enteral nutrition* 2008;32(2):160-8.

244. Pia de la Maza M, Gotteland M, Ramirez C, Araya M, Yudin T, Bunout D, et al. Acute nutritional and intestinal changes after pelvic radiation. *Journal of the American College of Nutrition* 2001;20(6):637-42.

245. Yeoh E, Horowitz M, Russo A, Muecke T, Robb T, Maddox A, et al. Effect of pelvic irradiation on gastrointestinal function: a prospective longitudinal study. *The American journal of medicine* 1993;95(4):397-406.

246. Pouteau E, Nguyen P, Ballevre O, Krempf M. Production rates and metabolism of short-chain fatty acids in the colon and whole body using stable isotopes. *The Proceedings of the Nutrition Society* 2003;62(1):87-93.

247. Isenring EA, Capra S, Bauer JD. Nutrition intervention is beneficial in oncology outpatients receiving radiotherapy to the gastrointestinal or head and neck area. *Br J Cancer* 2004;91(3):447-52.

248. Ravasco P, Monteiro-Grillo I, Vidal PM, Camilo ME. Dietary counseling improves patient outcomes: a prospective, randomized, controlled trial in colorectal cancer patients undergoing radiotherapy. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2005;23(7):1431-8.

249. Ravasco P, Monteiro-Grillo I, Camilo M. Individualized nutrition intervention is of major benefit to colorectal cancer patients: long-term follow-up of a randomized controlled trial of nutritional therapy. *Am J Clin Nutr* 2012;96(6):1346-53.

250. Isenring EA, Bauer JD, Capra S. Nutrition support using the American Dietetic Association medical nutrition therapy protocol for radiation oncology patients improves dietary intake compared with standard practice. *Journal of the American Dietetic Association* 2007;107(3):404-12.

251. Wanders AJ, van den Borne JJ, de Graaf C, Hulshof T, Jonathan MC, Kristensen M, et al. Effects of dietary fibre on subjective appetite, energy intake and body weight: a systematic review of randomized controlled trials. *Obesity reviews : an official journal of the International Association for the Study of Obesity* 2011;12(9):724-39.

252. Clark MJ, Slavin JL. The effect of fiber on satiety and food intake: a systematic review. *Journal of the American College of Nutrition* 2013;32(3):200-11.

253. Ross AB. Present status and perspectives on the use of alkylresorcinols as biomarkers of wholegrain wheat and rye intake. *Journal of nutrition and metabolism* 2012;2012:462967.

APPENDICES

APPENDIX 1

Study interventional documentation

1. **Fibre in Foods Guideline booklet: example pages**
2. **Ease of Use questionnaire for guidance booklet**
3. **7 Day Food Diary (A4 version)**
4. **Exchange diary: examples pages**

The Royal Marsden NHS Foundation Trust

Department of Nutrition and Dietetics

FIBRE IN FOOD BOOKLET

(Study Version)

Date: October 2009 **Version:** *v.2*

CONTENTS

Cakes and Pastries

Description	Portion size	Points
Almond slice	One (35g)	0.5
Apple turnover / Strudle	One (100g)	0.5
Banana Bread	One average slice (85g)	0.5
Bakewell tart	One (43g)	1.0
Chelsea bun	One (78g)	1.5
Cherry slice / cake	One (40g)	0.5
Carrot cake	One large slice (85g)	1.0
Currant bun / Hot Cross Bun	One (60g)	3.0
Custard tart	One individual (94g)	1.0
Custard Slice	One large slice (140g)	1.5
Danish-style pastry	One average sized pastry (55g)	1.0
Doughnut - jam	One (75g)	0.5
Doughnut - ring	One (60g)	0.5
Drop scones / Scotch pancakes	One (31g)	0.5
Eccles cake	One (45g)	0.5
Éclairs (and other fresh cream cakes)	One	None
Flapjacks	See 'biscuits'	-
Fruit cake / Christmas cake	One slice (70g)	1.0
Greek style pastries (baklava)	One small	0.5
Iced Bun	One (65g)	0.5
Jam tart	One (34g)	0.5
Macaroon / coconut pyramid	One (28g)	1.0
Malt Loaf with fruit	One small slice (35g)	1.0
Mince Pie	One (55g)	1.0
Muffins – American style / Seeded	One (85g)	1.5
Pancakes	One medium pancake (110g)	1.0
Rock cakes	One medium (60g)	1.0
Scones – fruit, plain, cheese	One (48g)	1.0
Sponge cakes: Chocolate, gateau, mini (Swiss) rolls, ginger, lemon drizzle, Madeira, Battenberg, Cup cakes	One individual cake or one average slice (60g)	0.5
Teacake	One (55g)	1.7
Welsh cakes	One (28g)	0.5

USING FOOD LABELS

Most foods have their nutritional content (including their fibre content) detailed in a label on the wrapper or packaging. The following label shows the nutritional breakdown of a packet of crisps and tells you how much fibre is in the whole bag (34.5g) or 100g.

TYPICAL NUTRITIONAL VALUES		
	Per 34.5g pack	Per 100g
Energy	725 kJ 180 kcal	2181 kJ 523 kcal
Protein	2.0 g	5.8 g
Carbohydrate of which sugars	17.7 g 0.7 g	51.3 g 1.9 g
Fat of which saturates of which mono-unsaturates of which polyunsaturates	11.3 g 0.9 g 9.2 g 0.7 g	32.7 g 2.5 g 26.6 g 2.1 g
Fibre	1.4 g	4.1 g
Sodium*	0.19 g	0.55 g
*Equivalent as salt	0.48 g	1.40 g

1. One ***point*** of Fibre equals one ***gram*** of fibre. We would like you to estimate your fibre intake to the nearest gram or half gram, so if you ate the whole packet of crisps (above) this would amount to 1.5 grams.

2. For all other foods, look at the label which will tell you how many grams (or points) of fibre the item of food contains. Then, tot-up or estimate the amount of food you have eaten.

a) If you eat ***MORE*** than the typical serving: e.g. If you ate ***TWICE*** as much as the typical serving, double the number of grams (or points) of fibre you actually consumed.

b) If you eat ***LESS (e.g. half)*** of a typical serving: divide by 2 to give you the number of grams (or points) of fibre you actually consumed.

Questionnaire:

How easy was it to use the Fibre in Foods booklet?

Please complete all questions

Questionnaire: Ease of use of the Fibre in Foods booklet

Section 1 – General layout and design (please tick one box)

Which size of booklet did you use?

☐ Large size only ☐ Small size only ☐ Both sizes

Was the design and organisation of the booklet easy to follow?

☐ Very easy ☐ Quite easy ☐ Undecided ☐ Quite difficult ☐ Very difficult

Could the design be improved and if so, how (please comment below)?

1. _____

2. _____

3. _____

4. _____

5. _____

Would you recommend this booklet to others if they wanted to estimate their fibre intake?

☐ Definitely 'yes' ☐ Maybe 'yes' ☐ Undecided ☐ Maybe 'No' ☐ Definitely 'No'

Section 2 – Completeness (Please tick one box)

In general, were you able to find the fibre content of the foods that you ate?

☐ yes, always ☐ yes, mostly ☐ Undecided ☐ No, partly ☐ No, never

Were there any foods which you ate which you could not find (please list below)?

1. _____

2. _____

3. _____

4. _____

5. _____

6. _____

7. _____

8. _____

9. _____

10. _____

Section 3 – Accuracy and use of Food Labels (Please tick one box)

Did you weigh any items before recording your fibre intake?

☐ yes, many times ☐ yes, a few times ☐ No, never

If you did weigh any items, please list which these were below?

1. _____

2. _____

3. _____

4. _____

5. _____

Did you ever use food labels (rather than the booklet) to estimate your fibre points?

☐ A lot	☐ A little	☐ Never	☐ Never
(over 50% of the time)	(less than 50% of the time)	(I did not have time)	(I didn't need to)

Many thanks for completing this form. Please return it to by hand or by post to:

Linda Wedlake (Research Dietitian)

Department of Nutrition and Dietetics, The Royal Marsden NHS Foundation Trust, Downs Road, Sutton. SM2 5PT

Date (enter date)

Dear (enter patient's name)

7 DAY FOOD DIARY

This diary is designed to obtain accurate information about the type and quantity of food that you eat.

Please return to:

Linda Wedlake
Research Dietitian
Nutrition & Dietetics
The Royal Marsden Hospital
Sutton
Surrey
SM2 5PT

For research personnel use only:

DIETPLAN Registration no.: _____

Date of entry: _____

Assessment type: _____

Activity level (recreational): _____

Activity level (occupational): _____

Patient Details

Name: ……

Date: ……

Weight: ……

Height: ……

Date of birth: ……..

GENERAL QUESTIONS

Which type of bread do you **usually** eat?

White	
Brown/Hovis	
Granary	
Wholemeal	
None	

Do you **usually** buy large or small loaves, sliced or unsliced?

Large	
Small	
Sliced	
Unsliced	

If you eat any type of biscuit regularly, please specify which brands:

……
……
……

Which type of milk do you **usually** use?

Full cream milk	
Semi-skimmed milk	
Skimmed milk	
Soya milk	
Lactose-free	
None	

How much milk do you **usually** use?

1-2 pints daily	☐
½ -1 pint	☐
¼ - ½ pint	☐
None	☐

How many tablespoons of milk do you take in tea and coffee?

…… tablespoons in a cup of tea

…… tablespoons in coffee

None: Tea/Coffee* taken black

*please circle if applicable

Which kind of fat do you usually use on bread, toast etc?

Butter	☐	
Margarine	☐	
Low fat	☐	spread

Which brand do you usually use?

……..

Which kind of fat do you usually use when cooking?

Butter	☐
Olive Oil	☐
Vegetable oil	☐
Lard	☐
Other …….	☐

What do you do with the visible fat on meat?

Eat most of the fat	
Eat as little as possible	
Eat some of the fat	
Don't eat meat	

How often do you eat food that is fried?

Daily	
4-6 times/week	
1-3 times/week	
Less than once/week	

Do you drink alcoholic drinks?

YES ☐ NO ☐

If the answer is YES, please indicate how many units you drink/week.
(**i.e. 1 unit = ½ pint beer/lager or 1 small glass wine or 1 tot spirit)**

…… units/week

FOOD RECORD

Read these instructions and the example carefully once or twice before you start.

We would like you to record, as accurately as possible, what you eat and drink for 7 days.

- Please record **ALL** food and drink consumed. Record at the time of eating and **NOT** from memory at the end of the day. Keep this record sheet with you throughout the day.

- You should include all meals and snacks, plus sweets, drinks etc. When recording food eaten at meals, please include any sauces, dressings or extras, e.g. gravy, salad dressing, pickles as well as the main food.

If you do not eat a particular meal or snack simply draw a line across the page at this point.

Guidelines for describing food & drink:

1. Please give details of the cooking method i.e. grilled, boiled, roasted, fried.

2. Give as many details as possible about the food:

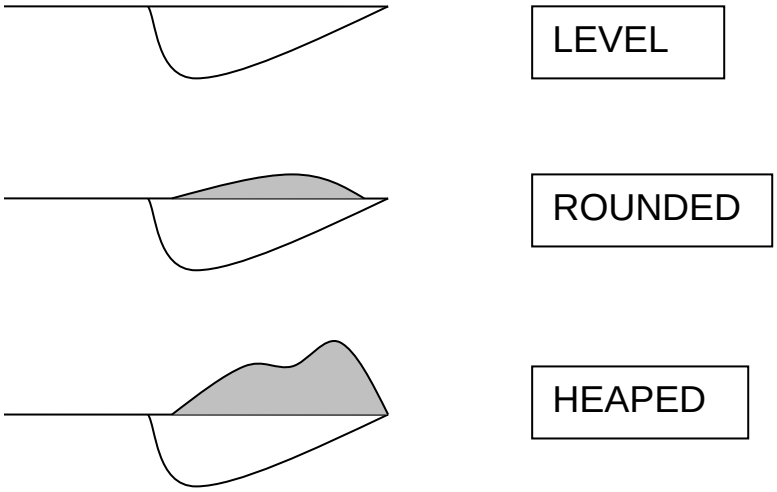
   a) State brand name if applicable
      → i.e. 'Heinz' baked beans OR
      'John West' tuna chunks in brine

   b) Name the type of biscuit, cake or cereal
      → i.e. Chocolate Hob-Nob, Madeira, Branflakes

   c) Name the type of cheese, fish or meat
      → i.e. Red Leicester cheese, smoked haddock fillet, lamb chop

3. Suggestions for recording quantity of food and drink:

   a) For many foods (vegetables, cereals and some fruit) a household measure is adequate, i.e. state the number of teaspoons (tsp), tablespoons (tbsp) or cups. Also whether it is level, rounded or heaped.



   b) All convenience foods have their weight on the packaging and this can be quoted i.e. 150g carton Ski raspberry yoghurt OR ½ 440g tin of Heinz Tomato soup.

   c) Bread, fruit loaves etc. please indicate the size of loaf and thickness of the slice i.e. 1 thick slice granary bread, small loaf.

   d) Cheese, fish, meat : if possible please weigh your portions.

      Otherwise describe as well as you can i.e.
      - 2 large thin slices ham
      - 2 small pork chops (no fat)
      - Matchbox sized cube of cheddar cheese.

Remember to include everything you eat and drink including snacks, nibbles and food grabbed whilst out of the house.

Please do not change what you normally eat just because you are filling out this record. We want to see what is **normal** in your daily life.

When recording home-made foods, please list all ingredients used in recipe and estimate how much of each ingredient was consumed in the portion of food you ate.

The example on the following pages may be useful as a guide but please remember that although we have included space to record all possible meals and snacks, this does not mean that you have to eat at these specific times.

If you do not have very regular meals, please try to record the food you eat throughout the day, starting with the first items you eat and continuing to the last item consumed before bedtime.

THANK YOU VERY MUCH FOR YOUR HELP.

DIETARY RECORD SHEET – EXAMPLE

- Record **ALL** food and drink consumed during the day including snacks, nibbles, sauces and dressings.
- Record method of cooking, type and quantity of food.
- For home-made meals, please record all ingredients and the quantity of these consumed.

DAY: ……..... **DATE: ……..**

MEAL/ SNACK	QUANTITY EATEN	DETAILS	Food Code: (leave blank)
Early morning	1 cup 1 tbsp 1 tsp	Tea Semi-Skimmed milk Granulated sugar	
Breakfast	3 heaped tbsp ¼ pint 1 thick slice 1 rounded tsp 1 heaped tsp 2 mugs	Branflakes (Kellogg's) Full cream milk (for cereal & drink) Poppy seed bread (small loaf, self cut) 'Olivio' margarine Thick cut marmalade (Tesco's own) Coffee	
During morning	85g 330ml can	Vanilla flavour bio-yoghurt (Shape) Coca cola	
Lunch	1 standard 2 tbsp 2 thin strips 1 large 1 large mug	Onion bagel, toasted Full fat cream cheese (Philadelphia) Smoked salmon Banana Hot chocolate (Cadbury's)	

MEAL/ SNACK	QUANTITY EATEN	DETAILS	Food Code: (leave blank)
During Afternoon	1 tall glass 1 small	Orange squash (Robinson's) Blueberry muffin (Sainsbury's)	
Evening meal	4 heaped tbsp 2 drumsticks 1 tbsp 1 tbsp 3 tbsp 3 heaped tbsp 1 tbsp 2 tbsp 2 small glass	Chicken casserole (homemade with tomato/wine based sauce) containing: Chicken, baked (no skin) Olive oil Red wine Chopped fresh tomatoes Courgettes Carrots Boiled white long grain rice Orange juice	
During evening	4 squares 2 cups 2 tbsp 2 tsp	Cadbury's Fruit & Nut chocolate Tea Semi-skimmed milk Granulated sugar	
Bedtime			

DIETARY RECORD SHEET

- Record **ALL** food and drink consumed during the day including snacks, nibbles, sauces and dressings.
- Record method of cooking, type and quantity of food.
- For home-made meals, please record all ingredients and the quantity of these consumed.

DAY 1: ……..... DATE: ……..

MEAL/ SNACK	QUANTITY EATEN	DETAILS	Food Code: (leave blank)
Early morning			
Breakfast			
During morning			
Lunch			

MEAL/ SNACK	QUANTITY EATEN	DETAILS	Food Code: (leave blank)
During Afternoon			
Evening meal			
During evening			
Bedtime			

DIETARY RECORD SHEET

- Record **ALL** food and drink consumed during the day including snacks, nibbles, sauces and dressings.
- Record method of cooking, type and quantity of food.
- For home-made meals, please record all ingredients and the quantity of these consumed.

DAY 2: ……..... DATE: ……..

MEAL/ SNACK	QUANTITY EATEN	DETAILS	Food Code: (leave blank)
Early morning			
Breakfast			
During morning			
Lunch			

MEAL/ SNACK	QUANTITY EATEN	DETAILS	Food Code: (leave blank)
During Afternoon			
Evening meal			
During evening			
Bedtime			

DIETARY RECORD SHEET

- Record **ALL** food and drink consumed during the day including snacks, nibbles, sauces and dressings.
- Record method of cooking, type and quantity of food.
- For home-made meals, please record all ingredients and the quantity of these consumed.

DAY 3: ……..... DATE: ……..

MEAL/ SNACK	QUANTITY EATEN	DETAILS	Food Code: (leave blank)
Early morning			
Breakfast			
During morning			
Lunch			

MEAL/ SNACK	QUANTITY EATEN	DETAILS	Food Code: (leave blank)
During Afternoon			
Evening meal			
During evening			
Bedtime			

DIETARY RECORD SHEET

- Record **ALL** food and drink consumed during the day including snacks, nibbles, sauces and dressings.
- Record method of cooking, type and quantity of food.
- For home-made meals, please record all ingredients and the quantity of these consumed.

DAY 4: …….. DATE: ……..

MEAL/ SNACK	QUANTITY EATEN	DETAILS	Food Code: (leave blank)
Early morning			
Breakfast			
During morning			
Lunch			

MEAL/ SNACK	QUANTITY EATEN	DETAILS	Food Code: (leave blank)
During Afternoon			
Evening meal			
During evening			
Bedtime			

DIETARY RECORD SHEET

- Record **ALL** food and drink consumed during the day including snacks, nibbles, sauces and dressings.
- Record method of cooking, type and quantity of food.
- For home-made meals, please record all ingredients and the quantity of these consumed.

DAY 5: ……..... DATE: ……..

MEAL/ SNACK	QUANTITY EATEN	DETAILS	Food Code: (leave blank)
Early morning			
Breakfast			
During morning			
Lunch			

MEAL/ SNACK	QUANTITY EATEN	DETAILS	Food Code: (leave blank)
During Afternoon			
Evening meal			
During evening			
Bedtime			

DIETARY RECORD SHEET

- Record **ALL** food and drink consumed during the day including snacks, nibbles, sauces and dressings.
- Record method of cooking, type and quantity of food.
- For home-made meals, please record all ingredients and the quantity of these consumed.

DAY 6: ……..... DATE: ……..

MEAL/ SNACK	QUANTITY EATEN	DETAILS	Food Code: (leave blank)
Early morning			
Breakfast			
During morning			
Lunch			

MEAL/ SNACK	QUANTITY EATEN	DETAILS	Food Code: (leave blank)
During Afternoon			
Evening meal			
During evening			
Bedtime			

DIETARY RECORD SHEET

- Record **ALL** food and drink consumed during the day including snacks, nibbles, sauces and dressings.
- Record method of cooking, type and quantity of food.
- For home-made meals, please record all ingredients and the quantity of these consumed.

DAY 7: …….. DATE: ……..

MEAL/ SNACK	QUANTITY EATEN	DETAILS	Food Code: (leave blank)
Early morning			
Breakfast			
During morning			
Lunch			

MEAL/ SNACK	QUANTITY EATEN	DETAILS	Food Code: (leave blank)
During Afternoon			
Evening meal			
During evening			
Bedtime			

Notes

- Use this page to make any notes or comments that may be helpful in interpreting your food diary.

Notes

- Use this page to make any notes or comments that may be helpful in interpreting your food diary.

Notes

- Use this page to make any notes or comments that may be helpful in interpreting your food diary.

Fibre Exchange Diary – Example pages

High (un-shaded) and Low (shaded) Fibre versions

Booklet printed in A5 size (8 pages)

WEEK 7 OF RADIOTHERAPY

Day 1 (Date:)

☐ ☐

Day 2

☐ ☐

Day 3

☐ ☐

Day 4

☐ ☐

Day 5

☐ ☐

Day 6

☐ ☐

Day 7

☐ ☐

ANY QUESTIONS?

If you have any questions at all on the study including help in completing
this booklet or questions on the Fibre in Food Booklet, call:

Linda 020 8642 6011 (ext. 1455)

FIBRE POINTS DIARY

Below is your fibre prescription, in other words, the total amount of fibre that we have asked you to consume as part of this study.

Name:_____

Fibre prescription (Points/day): _____

Please record the number of fibre points that you consume each day by placing a tick in a box each time you consume one fibre point.

REMEMBER: One box = One fibre point (or 'gram')

The number of boxes on each line is equal to the number of fibre points we have asked you to eat each day. If you eat more points than this, add further boxes and tick them. Please do not use the boxes for the next day. If you eat half a fibre point, place a line through the box and tick as shown:

Half-point ☐
Two half-points (i.e. one point) ☐

WEEK 7 OF RADIOTHERAPY

Day 1 (Date:)

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

Day 2

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

Day 3

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

Day 4

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

Day 5

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

Day 6

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

Day 7

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

ANY QUESTIONS?

If you have any questions at all on the study including help in completing
this booklet or questions on the Fibre in Food Booklet, call:

Linda 020 8642 6011 (ext. 1455)

FIBRE POINTS DIARY

Below is your fibre prescription, in other words, the total amount of fibre that we have asked you to consume as part of this study.

Name:_____

Fibre prescription (Points/day): _____

Please record the number of fibre points that you consume each day by placing a tick in a box each time you consume one fibre point.

REMEMBER: One box = One fibre point (or 'gram')

The number of non-shaded boxes on each line is equal to the number of fibre points we have asked you to eat each day. If you eat more points than this, use the further shaded boxes and tick them. If you eat half a fibre point, place a line through the box and tick as shown:

Half-point ☐
Two half-points (i.e. one point) ☐

APPENDIX 2

Study ethics documentation
RMH versions

1. **CCR 3142 'Fibre Study' Consent Form**
2. **Patient Information Sheet**
3. **GP Letter**
4. **Case Report Form (CRF)**
5. **Cost questionnaire**

Centre No:
Study Protocol Number:
Ethics Protocol Number:
Patient Identification No. for this trial:

CONSENT FORM

Title of Project:
A randomised controlled trial to investigate the role of low or high fibre diets in patients undergoing pelvic radiotherapy.

Name of Principal Investigator: Dr. Jervoise Andreyev

Please Tick Box

1. I confirm that I have read and understand the information sheet dated ……..(version……) for the above study and that I have had an opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving a reason, and my medical care and legal rights will not be affected. ☐
3. I am willing to allow access to my medical records to check that the study is being carried out correctly. I have been assured that strict confidentiality will be maintained. ☐
4. I agree for my GP to be notified of my participation in this study. ☐
5. I agree to participate in the above study. ☐
6. I would/would not like to be informed of the results of this study. (please delete as appropriate).

Name of Patient	Date	Signature
Name of Person obtaining consent (if different from Principal Investigator)	Date	Signature
Principal Investigator	Date	Signature

1 copy for Patient, 1 for Principal Investigator, 1 for Hospital Note

Patient Information Sheet

The Royal Marsden NHS
NHS Foundation Trust

The Fibre study.
A randomised controlled trial to investigate the role of low or high fibre diets in patients undergoing pelvic radiotherapy.

Introduction
We would like to invite you to take part in a research study. Before you decide, it is important for you to understand why the research is being done, and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your GP if you wish. Ask us if there is anything that is not clear to you or if you would like more information. Take time to decide whether you or not you wish to take part. Thank you for reading this.

Why am I being invited to take part?
You have been diagnosed with cancer of a pelvic origin and after discussion with you, radiotherapy has been chosen as an appropriate treatment. This study will recruit men and women who will receive radiotherapy for cancers in the urinary tract or of a gynaecological origin or arising from the bowel, colon, rectum or anus.

What is the purpose of the study?
The study has two major objectives. The first is to see whether altering the amount of fibre in the diet during your treatment makes a difference to any bowel side effects you develop. The second is to see whether the amount of bowel that receives a particular dose of radiotherapy alters the symptoms that patients may experience.

1) Effect of dietary fibre on gastrointestinal side effects:
Over the last few years, considerable progress has been made in the way in which radiotherapy treatment is given. However, despite new ways of giving treatment more accurately to the tumour, we cannot completely protect healthy areas of the body, which lie close to the tumour, from the radiotherapy beams. During treatment for tumours in the pelvis, the gastrointestinal tract can become inflamed resulting in side effects such as loose stool, diarrhoea, having to rush to the lavatory and sometimes problems with being able to control the bowel. Our research indicates that up to 90% of patients develop changes in the way the bowel behaves during radiotherapy and 50% of patients state that these bowel changes are ‘moderate’ or ‘severe’.

For several years our research team has been seeing how we can use changes in diet during radiotherapy to protect the healthy gastrointestinal tract from the side effects of treatment. In this study, we want to see whether diets high in fibre or diets low in fibre are better for patients who are having radiotherapy. In the past, radiotherapy departments usually advised a low fibre diet during treatment but the potential benefits of this advice have never been properly tested. A high fibre diet might also be helpful but again, this has yet to be properly tested. If we were able to show that either a high or low fibre diet offered protection against unwanted changes in bowel habit during radiotherapy then we could advise future patients as to how best to change their fibre intake to reduce the risk of side-effects. Preventing symptoms that occur during treatment may make treatment easier to carry out and may also reduce the risk of long term problems.

2) Amount of bowel within the treatment field:
In addition to assessing the effect of fibre on bowel symptoms, in a sub-set of patients with gynaecological or gastrointestinal tumours, we want to see whether there is a link between

the amount of bowel exposed to the radiotherapy and the risk of getting gastrointestinal side-effects.

Do I have to take part?
It is up to you to decide whether or not to take part. If you decide to take part, you will be given this information sheet to keep, and be asked to sign a consent form. If you decide to take part, you are still free to change your mind or withdraw at any time without giving a reason. Your usual treatment plan will not be affected in any way.

What will happen to me if I take part?
If you decide to take part in this study, you will be assigned to one of three groups at random. This means you will be encouraged to stay on your normal diet, or to go onto a low fibre diet or to go onto a high fibre diet. Neither you nor the staff looking after you can choose which group you are put into. The type of diet you will be asked to follow will be chosen by computer. This helps avoid any bias that you or the staff may have from preconceived ideas about which treatment is best. Patients in each group will have a different treatment and then the results are compared. This is called a randomised trial.

A trained dietitian will discuss with you the amount of fibre that we would like you to eat once we know which group you will be joining. If the computer has chosen a group for you which requires you to eat more or less fibre than normal, you will be given a Food Fibre Content booklet to enable you to estimate how much fibre is contained within the foods you normally eat and we will ask you to stick to your new fibre intake for the duration of your radiotherapy. We will not change any other aspect of your diet. If possible, we would like you to trial your new fibre intake and get familiar with the Food Fibre Content booklet in advance of your radiotherapy. This will ensure that we are able to discuss any problems that you may have on your first day of radiotherapy when we will meet with you and ask you to start eating your 'prescribed' amount of fibre. You may be allocated to a group where you are asked to continue with your normal diet and not make changes to your intake of fibre.

During the first and last week of your radiotherapy we will ask you to record everything you eat and drink for 7 days. We will also meet with you once a week during treatment to give you advice about your diet and see how you are managing. At these meetings we will ask you to remember what you have eaten on the previous day and also ask you to complete a simple questionnaire about any symptoms you are experiencing.

In addition to following the diet which has been chosen for you, we will also ask you to complete a daily 'Stool Chart' throughout your radiotherapy treatment. Finally, we will also ask you to tell us about any costs you may have incurred in dealing with symptoms that you might have experienced. If you are in one of the groups in which you have changed your fibre intake, we will also ask you about the costs (if any) that you might have noticed in following the new diet and also ask you how palatable you found the change in diet.

If you are a patient with a gynaecological or gastrointestinal tumour you may be asked to allow us to perform three additional CT scans during your treatment. This will allow us to see how much bowel is receiving radiotherapy. The scan is similar to previous CT scans you will have had to assess the tumour. The only possible difference is that beforehand you will be asked to drink a pint of a special drink with a orangey / lemony flavour that helps us to outline your bowel and allows us to take accurate measurements.

Finally, we will ask you to give us a blood sample at the start, midway through, at the end of radiotherapy and one year later. These (small) samples will be taken if possible at the same time as the routine blood tests which you will have during your treatment. We will also ask you to provide us with a (small) stool sample. Both of these items will enable us to investigate more closely the changes that occur during radiotherapy.

Are there any possible side-effects of participating in this study?

1) The effects of a change in dietary fibre:
You may experience a change in bowel habit as a result of changing your fibre intake. However your radiotherapy treatment will not be affected. Our fibre intervention is based on normal dietary foods rather than supplements and so your bowels should acclimatise gradually to the change without any side effects.

2) The effects of the additional CT scans for the Bowel Volume Group:
The additional dose of radiation that will be delivered as a result of the three extra scans that you will receive is very small compared to the overall dose of radiation that you will receive for your treatment. We are all exposed to a certain amount of background radiation and the additional dose that will be received resulting from the additional scans is equivalent to not more than 6 years' worth of normal background radiation.

3) Blood samples:
There is a very small risk of bruising when a blood sample is taken.

What are the possible disadvantages of taking part?
The main disadvantage is that if you are assigned to study groups in which you need to change the amount of fibre in your diet, you might need to spend some time planning and obtaining foods to eat to make this change. The Stool Chart takes a couple of minutes to complete each day. Once a week during your treatment (and at the very end of treatment) we will ask you to spend an additional 10 – 15 minutes with us discussing your dietary and fibre intake and ask you to complete some simple symptom and cost questionnaires. If you are in the group asked to have the additional scans, you will have to spend an additional hour in the hospital on those days after your normal radiotherapy treatment.

What are the possible benefits of taking part?
There are no direct benefits to you in taking part in the study. However your participation will enable us to collect important data that in the longer term will allow us to givedeliver improved advice to future patients. It will also enable us to better understand the relationship between the amount of bowel that receives radiotherapy and the risk of side effects.

Will my taking part in this study be kept confidential?
Yes

Who is organising and funding the research?
This study is organised by the Royal Marsden NHS Trust jointly by the Departments of Rehabilitation and Radiotherapy. The Royal Marsden Charitable Trustees have kindly agreed to meet the costs of the study.

Who has reviewed the study?
The scientific quality of the study has been reviewed by the Royal Marsden/Institute of Cancer Research Committee for Clinical Research, and ethical approval has been granted by the Royal Marsden Research Ethics Committee.

Further information
Before you make a decision about your participation in this study, the study doctor is available to answer any questions you may have and to explain the study. Allow yourself as much time as you need to think through your decision. If you then decide that you still wish to take part, your doctor will ask you to confirm in writing that you have read and understand

this patient information, that all your questions have been answered completely and that you wish to continue with the study.

If you have any questions please call Dr Peter Blake, Consultant Clinical Oncologist (Gynaecology) Tel: 0207 808 2581 or Dr HJN Andreyev, Consultant Gastroenterologist in Pelvic Radiation Disease, Tel: 020 7811 8216 or Ms Linda Wedlake, Research Dietitian, Tel: 020 8642 6011 (ext. 1455) who will be happy to discuss the study with you.

Thank you for considering taking part in this study.

Date given to patient: _____

GP letter

Title: A randomized controlled trial to investigate the role of low or high fibre diets in patients undergoing pelvic radiotherapy

Dear Doctor _____,

Your patient, _____, has kindly agreed to take part in the above research study. A patient information sheet is attached for your information.

If you have any questions, or would like further information, please contact Dr. HJN Andreyev (Tel: 020 7811 8216) or Ms Linda Wedlake (Tel: 020 8642 6011, ext. 1455).

Yours sincerely

Dr HJN Andreyev
Consultant Gastroenterologist in Pelvic Radiation Disease

CCR 3142 'Fibre Study' - CASE REPORT FORM

Section 1: Patient's Details

Age: _____ Gender: _____

Diagnosis: ☐ Gynaecological ☐ Colorectal/anal ☐ Urological (bladder)

☐ Ovarian ☐ Colorectal

☐ Endometrial ☐ Anal

Other: _____ _____

RMH Consultant: _____

Section 2: Screening / Eligibility

Patient meets eligibility/exclusion criteria (refer to protocol) ☐ yes

Patient able to give informed consent ☐ yes

Section 3.1: Consent / Randomisation

Date patient consented: _____

Consent form completed: ☐ yes

Date randomised: _____

GP letter sent: ☐ yes

HIS (CCRPAT) entry: ☐ yes

Study Group: ☐ Grp.1 (Low) ☐ Grp.2 (High) ☐ Grp.3 (Normal)

Stratification: ☐ Gynaecological ☐ Colorectal/anal ☐ Urological (bladder)

Concomittant chemo: ☐ Yes ☐ No

Food Fibre Content Booklet given (Groups 1 and 2 only): ☐ yes

Bowel Volume Group: ☐ No ☐ Yes (Complete section 6)

Section 3.2: Withdrawal

Patient withdrawn from study: ☐ yes

Expressed wish to withdraw ☐ yes

Radiotherapy cancelled ☐ yes

Other Reason (Please state): _____

_____

Date withdrawn: _____

CCR PAT completed (date): _____

(Please note that patients should only be withdrawn from the study if their radiotherapy has been cancelled for clinical reasons, or they wish to withdraw from all further data collection. Patients who are not following the prescribed diet but who are still willing to participate in data collection are not counted as withdrawals.)

Section 4.1: Treatment Data - Radiotherapy Prescription

Phase 1: Dose (Gy): _____ Fraction size: _____ No. treatments: _____

Phase 2: Dose (Gy): _____ Fraction size: _____ No. treatments: _____

Phase 3: Dose (Gy): _____ Fraction size: _____ No. treatments: _____

TOTAL (EBRT) Dose: _____ Brachytherapy: ☐ yes ☐ No

Radiotherapy start date: _____ Completion date: _____

Special procedures (e.g. bladder-filling): _____

_____

Section 4.2: Treatment Data - Chemotherapy / Other medications

Chemotherapy regimen:

Pre- or post-RT only ☐ yes

Concomitant ☐ yes

Concomitant + pre- and/or post-RT ☐ yes

Name:_____ Dose: _____

Pre-RT: ☐ yes During-RT: ☐ yes

Name:_____ Dose: _____

Pre-RT: ☐ yes During-RT: ☐ yes

Other relevant medications (e.g. statins, bowel agents)

Name:_____ Dose: _____

Pre-RT: ☐ yes During-RT: ☐ yes

Name:_____ Dose: _____

Pre-RT: ☐ yes During-RT: ☐ yes

Name:_____ Dose: _____

Pre-RT: ☐ yes During-RT: ☐ yes

Section 5.1: Measurements: RT Day 1, Week 1 (Baseline)

Day / date: _____ RT # Number: _____

Weight (kg):_____ Height (m): _____ BMI (kg/m^2):_____

7d Food Diary given: ☐ yes

IBDQ (Baseline) completed: ☐ yes

IBDQ score: _____ IBDQ-B score: _____

Bristol Stool Chart given: ☐ yes ☐ no

Groups 1 (Low) and 2 (High) only:

Reinforce fibre advice: ☐ yes ☐ no

Blood sample taken: ☐ yes ☐ no

Stool sample received: ☐ yes ☐ no

Time taken for interview (mins): _____ Interviewer's initials: _____

Section 5.2: Measurements: RT Day 6, Week 2

Day / date: _____ RT # Number: _____

7d Food Diary collected: ☐ yes ☐ no

Average daily fibre intake (g): _____ Range (g): _____

Averaged daily intake (kcals): _____ Kcals/BMR: _____

%CHO: _____ %protein: _____ % fat:_____

IBDQ (week 1) completed: ☐ yes

IBDQ score: _____ IBDQ-B score: _____

Bristol Stool Chart (results week 1):

Number of days toxicity: _____
(stool frequency >3 events of type 6 or 7 / day for >2 days, or use of medication):

Groups 1 (Low) and 2 (High) only:

Reinforce fibre advice: ☐ yes ☐ no

Cost questionnaire completed: ☐ yes ☐ no

Time taken for interview (mins): _____ Interviewer's initials: _____

Section 5.3: Measurements: RT Day 11, Week 3

Day / date: _____ RT # Number: _____

24 hour recall completed: ☐ yes ☐ no

Date / day of recalled intake: _____ Fibre intake (g): _____

IBDQ (week 2) completed: ☐ yes

IBDQ score: _____ IBDQ-B score: _____

Bristol Stool Chart (results week 2):

Number of days toxicity: _____
(stool frequency >3 events of type 6 or 7 / day for >2 days, or use of medication):

Groups 1 (Low) and 2 (High) only:

Reinforce fibre advice: ☐ yes ☐ no

Cost questionnaire completed: ☐ yes ☐ no

Blood sample taken: ☐ yes ☐ no

Stool sample received: ☐ yes ☐ no

Time taken for interview (mins): _____ Interviewer's initials: _____

Section 5.4: Measurements: RT Day 16, Week 4

Day / date: _____ RT # Number: _____

24 hour recall completed: ☐ yes ☐ no

Date / day of recalled intake: _____ Fibre intake (g): _____

IBDQ (week 3) completed: ☐ yes

IBDQ score: _____ IBDQ-B score: _____

Bristol Stool Chart (results week 3):

Number of days toxicity: _____
(stool frequency >3 events of type 6 or 7 / day for >2 days, or use of medication)

Groups 1 (Low) and 2 (High) only:

Reinforce fibre advice: ☐ yes ☐ no

Cost questionnaire completed: ☐ yes ☐ no

Time taken for interview (mins): _____ Interviewer's initials: _____

Section 5.5: Measurements: RT Day 21, Week 5

Day / date: _____ RT # Number: _____

24 hour recall completed: ☐ yes ☐ no

Date / day of recalled intake: _____ Fibre intake (g): _____

7d Food Diary given: ☐ yes

IBDQ (week 4) completed: ☐ yes

IBDQ score: _____ IBDQ-B score: _____

Bristol Stool Chart (results week 4):

Number of days toxicity: _____
(stool frequency >3 events of type 6 or 7 / day for >2 days, or use of medication)

Groups 1 (Low) and 2 (High) only:

Reinforce fibre advice: ☐ yes ☐ no

Cost questionnaire completed: ☐ yes ☐ no

Time taken for interview (mins): _____ Interviewer's initials: _____

Section 5.6: Measurements: RT Day 26, Week 6 (Do NOT complete for 25 treatments)

Day / date: _____ RT # Number: _____

7d Food Diary collected: ☐ yes ☐ no

Average daily fibre intake (g): _____ Range (g): _____

Averaged daily intake (kcals): _____ Kcals/BMR: _____

%CHO: _____ %protein: _____ % fat:_____

IBDQ (week 5) completed: ☐ yes

IBDQ score: _____ IBDQ-B score: _____

Bristol Stool Chart (results week 6):

Number of days toxicity: _____
(stool frequency >3 events of type 6 or 7 / day for >2 days, or use of medication)

Cost questionnaire completed: ☐ yes ☐ no

Section 5.6: Measurements: RT Day 26, Week 6 (continued)

Groups 1 (Low) and 2 (High) only:

Reinforce fibre advice: ☐ yes ☐ no

Time taken for interview (mins): _____ Interviewer's initials: _____

Section 5.7: Measurements: Exit Interview (RT Treatments: 25)

Day / date: _____ RT # Number: _____

Weight (kg):_____ Height (m): _____ BMI (kg/m^2):_____

Bristol Stool Chart (results week 5):

Number of days toxicity: _____
(stool frequency >3 events of type 6 or 7 / day for >2 days, or use of medication)

Patient reminded to post 7d Food Diary: ☐ yes ☐ no

Average daily fibre intake (g): _____ Range (g): _____

Averaged daily intake (kcals): _____ Kcals/BMR: _____

%CHO: _____ %protein: _____ % fat:_____

Cost Questionnaire (part 1) completed: ☐ yes ☐ no

Blood sample taken: ☐ yes ☐ no

Stool sample received: ☐ yes ☐ no

Groups 1 (Low) and 2 (High) only:

Cost questionnaire (part 2) completed: ☐ yes ☐ no

Palatability VAS completed: ☐ yes ☐ no

VAS score: _____

Time taken for interview (mins): _____ Interviewer's initials: _____

Section 5.8: Measurements: Exit Interview (RT Treatments: 28,30,31,32,34)

Day / date: _____ RT # Number: _____

Weight (kg):_____ Height (m): _____ BMI (kg/m^2):_____

24 hour recall completed: ☐ yes ☐ no

Date / day of recalled intake: _____ Fibre intake (g): _____

Bristol Stool Chart (results combined for weeks 6/7):

Number of days toxicity: _____
(stool frequency >3 events of type 6 or 7 / day for >2 days, or use of medication)

Cost Questionnaire (part 1) completed: ☐ yes ☐ no

Blood sample taken: ☐ yes ☐ no

Stool sample received: ☐ yes ☐ no

Groups 1 (Low) and 2 (High) only:

Cost questionnaire (part 2) completed: ☐ yes ☐ no

Palatability VAS completed: ☐ yes ☐ no

VAS score: _____

Time taken for interview (mins): _____ Interviewer's initials: _____

Section 5.9 Measurements: One year follow-up

Day / date: _____

IBDQ score: _____ IBDQ-B score: _____

Blood sample taken: ☐ yes ☐ no

Section 6: Bowel Volume Group

Planned radiation doses per volume of bowel (Gy) from patient's DVH

Dose (Gy)	Volume of bowel (cc) receiving this dose (% of total)	
	Small bowel	Large bowel
5		
10		
15		
20		
25		
30		
35		
40		

Section 6.1: Bowel Volume Group: CT 1

CT Scan 1 (Whole abdomin and pelvis @ 7.5mm slices)

Day / date: _____ RT # Number: _____

Total large bowel volume (cc): _____ Total small bowel volume (cc): _____

Total treated large bowel (cc): _____ Total treated small bowel (cc): _____

Section 6.2: Bowel Volume Group CT 2

CT Scan 2 (pelvis @ 7.5mm slices)

Day / date: _____ RT # Number: _____

Total treated large bowel (cc): _____ Total treated small bowel (cc): _____

Section 6.3: Bowel Volume Group CT 3

CT Scan 1 (pelvis @ 7.5mm slices)

Day / date: _____ RT # Number: _____

Total treated large bowel (cc): _____ Total treated small bowel (cc): _____

CCR 3142 'Fibre Study' - COST QUESTIONNAIRE

Part 0: Patient's Details

RMH Hospital Number: _____ Study number: _____

PART 1: ALL PATIENTS – WEEKLY COSTS OF SYMPTOM MANAGEMENT

Week 2, RT Day 6

In the last week have you:

Used pads for faecal incontinence: ☐ always ☐ sometimes ☐ never

Had extra laundry items due to accidents: ☐ >5 items ☐ 1-5 items ☐ none

Sought help from an NHS person for bowel problems: ☐ yes ☐ no

If 'yes' from whom? _____

Had extra travel costs because of bowel symptoms: ☐ yes ☐ no

If 'yes' can you estimate these costs? £_____

Purchased medication for bowel symptoms: ☐ yes ☐ no

If 'yes' can you estimate the costs? £_____

Incurred other symptom related costs (e.g. purchased new underwear or extra toilet paper)?:

☐ yes ☐ no

If 'yes': 1) What were these for? _____

2) About how much did they cost? £_____

Are you in paid employment? ☐ yes ☐ no

If 'yes' have you taken time off-work this week due to bowel symptoms?

☐ yes, most of the time ☐ yes, some of the time ☐ no

Have bowel symptoms prevented you from carrying out your normal activities this week?

☐ yes, most of the time ☐ yes, some of the time ☐ no

Week 3 and 4 RT Days 11 and 16

In the last week have you:

Used pads for faecal incontinence: ☐ always ☐ sometimes ☐ never

Had extra laundry items due to accidents: ☐ >5 items ☐ 1-5 items ☐ none

Sought help from an NHS person for bowel problems: ☐ yes ☐ no

If 'yes' from whom? _____

Had extra travel costs because of bowel symptoms: ☐ yes ☐ no

If 'yes' can you estimate these costs? £_____

Purchased medication for bowel symptoms: ☐ yes ☐ no

If 'yes' can you estimate the costs? £_____

Incurred other symptom related costs (e.g. purchased new underwear or extra toilet paper)?:

☐ yes ☐ no

If 'yes': 1) What were these for? _____

2) About how much did they cost? £_____

Are you in paid employment? ☐ yes ☐ no

If 'yes' have you taken time off-work this week due to bowel symptoms?

☐ yes, most of the time ☐ yes, some of the time ☐ no

Have bowel symptoms prevented you from carrying out your normal activities this week?

☐ yes, most of the time ☐ yes, some of the time ☐ no

EXIT INTERVIEWS (Delete as applicable):

Week 5, day 25, Week 6, day 28 OR day 30, Week 7, day 31 OR day 32 OR day 34

In the last week have you:

Used pads for faecal incontinence: ☐ always ☐ sometimes ☐ never

Had extra laundry items due to accidents: ☐ >5 items ☐ 1-5 items ☐ none

Sought help from an NHS person for bowel problems: ☐ yes ☐ no

If 'yes' from whom? _____

Had extra travel costs because of bowel symptoms: ☐ yes ☐ no

If 'yes' can you estimate these costs? £_____

Purchased medication for bowel symptoms: ☐ yes ☐ no

If 'yes' can you estimate the costs? £_____

Incurred other symptom related costs (e.g. purchased new underwear or extra toilet paper)?:

☐ yes ☐ no

If 'yes': 1) What were these for? _____

2) About how much did they cost? £_____

Are you in paid employment? ☐ yes ☐ no

If 'yes' have you taken time off-work this week due to bowel symptoms?

☐ yes, most of the time ☐ yes, some of the time ☐ no

Have bowel symptoms prevented you from carrying out your normal activities this week?

☐ yes, most of the time ☐ yes, some of the time ☐ no

PART 2: INTERVENTIONAL GROUPS 1 AND 2 ONLY

Part 2: Groups 1 and 2 only
As a result of following the study diet, have you noticed a change in:

Weekly food bill costs: ☐ increased ☐ reduced ☐ no effect

Time spent shopping: ☐ increased ☐ reduced ☐ no effect

Food preparation time: ☐ increased ☐ reduced ☐ no effect

Now that you have finished the study, do you intend to carry on with the diet?

☐ yes, all of the time ☐ yes, some of the time ☐ no ☐ don't know ☐ not sure

Would you recommend this diet to others?

☐ definitely, yes ☐ probably, yes ☐ don't know ☐ probably, no ☐ definitely, no

PART 3: INTERVENTIONAL GROUPS 1 AND 2 ONLY

Put a mark on the line below at a point which best describes how palatable you found the change in diet:

_____

Much worse than my normal diet	No different to my normal diet	Much better than my normal diet

APPENDIX 3

Gastrointestinal toxicity scoring tools

1. **Radiotherapy Oncology Group scoring tool (RTOG)**
2. **The Inflammatory Bowel Disease Questionnaire (IBDQ)**
3. **The Bristol Stool Form Scale in: The RMH Stool Chart**
4. **Instructions for collection of stool sample**

Radiotherapy Oncology Group (RTOG / EORTC) Toxicity Scoring for:

Lower GI including pelvis

Toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
LOWER GI INCLUDING PELVIS	No change	Increased frequency or change in quality of bowel habits not requiring medication/rectal discomfort not requiring analgesics	Diarrhoea requiring parasympatholytic drugs (e.g. Lomotil)/mucous discharge not necessitating sanitary pads/rectal or abdominal pain requiring analgesics	Diarrhoea requiring parenteral support/severe mucous or blood discharge necessitating sanitary pads, abdominal distension (flat plate radiograph demonstrated distended bowel loops)	Acute or subacute obstruction, fistula or perforation; GI bleeding requiring transfusion; abdominal pain or tenesmus requiring tube decompression or bowel diversion	Death

Inflammatory Bowel Disease Questionnaire (IBDQ)

In the last week please tell us how often you have:

		More than ever before	Extremely frequently	Very frequently	Moderate increase in frequency	Some increase in frequency	Slight increase in frequency	Not at all / normal
1	had your bowel open?							
2	felt tired and worn out?							
3	felt frustrated, impatient or restless?							
4	been unable to do what you want because of your bowels?							
5	had loose bowel movements?							
6	worried about your energy levels?							
7	worried about having to have something done about your bowels?							
8	you had to cancel an engagement because of your bowels?							
9	been troubled by pain in your bottom?							
10	felt generally unwell?							
11	worried about not being able to find a lavatory?							
12	been prevented doing leisure or sports by your bowels?							
13	been troubled by cramps in your tummy or bottom?							
14	been waking at night or having difficulty sleeping?							
15	been depressed or discouraged?							

Key: Highlighted questions constitute the Inflammatory Bowel Disease Questionnaire – Bowel Subset (IBDQ-B)

		More than ever before	Extremely frequently	Very frequently	Moderate increase in frequency	Some increase in frequency	Slight increase in frequency	Not at all / normal
16	not gone somewhere because there is no lavatory nearby?							
17	passed a large amount of gas							
18	worried about getting to the weight you would like							
19	worried about your illness							
20	been troubled by bloating							
21	been relaxed and free from tension							
22	had a problem with bleeding from your bottom?							
23	been embarrassed about your bowels?							
24	felt like you need to have your bowels open but nothing happens?							
25	felt tearful and upset?							
26	been troubled by accidental soiling?							
27	felt angry as a result of your bowel problems?							
28	felt limited in sexual activity because of your bowels?							
29	felt disgusted about your bowel problems?							
30	felt irritable?							
31	experienced a lack of understanding from others?							
32	felt satisfied, happy or pleased with your life?							

Key: Highlighted questions constitute the Inflammatory Bowel Disease Questionnaire – Bowel Subset (IBDQ-B)

THE ROYAL MARSDEN

Name: _____ **Hospital No:** _____

STOOL CHART

Bristol Stool Type No:

Type 1	 Separate hard lumps, like nuts (hard to pass)	Type 5	 Soft blobs with clear-cut edges (passed easily)
Type 2	 Sausage-shaped but lumpy	Type 6	 Fluffy pieces with ragged edges, a mushy stool
Type 3	 Like a sausage but with cracks on its surface	Type 7	 Watery, no solid pieces ENTIRELY LIQUID
Type 4	 Like a sausage or snake, smooth and soft	Reproduced by kind permission of Dr KW Heaton, Reader in Medicine at the University of Bristol	

Patient passes stool per:

rectum / colostomy / ileostomy
(circle as appropriate)

Key:

Colour:	Pale / Putty, Yellow, Green, Brown, Black
Blood:	Fresh / Old
Mucous:	Yes / No
Amount:	Volume e.g. mls or small / moderate / large + / ++ / +++

Date	Time	Colour	Type No	Blood	Mucus	Amount	**Comments:** e.g. smell, stool floating, GvHD, iron tablets, undigested food	**Used anti-diarrhoeal medication?**

Please enter time of event and every event per day, sheet continues overleaf. Please ask your study representative for additional sheets if required.

The Royal Marsden NHS
NHS Foundation Trust

Date: Enter date

Dear: Enter patient's name

Subject: Instructions for collecting your stool sample

Thanks so much for agreeing to do this! Instructions as follows:

1) Please wear a pair of disposable gloves.
2) Use the card tray to collect the stool before it drops into the pan.
3) Decant enough stool to fill the yellow-top container using the wooden spatula.
4) Place the yellow top container in the 'biochemistry' bag and seal the bag using the self-adhesive strip.
5) Dispose of any surplus stool and collection items.
6) Bring the sample with you when you come to your radiotherapy appointment and please ask the reception desk to call me when you arrive (ext. 1455).

Please fill the yellow topped container as otherwise we will not have enough stool sample to perform a complete analysis.

I look forward to collecting your sample and many thanks again.

With best wishes,

Linda Wedlake
Research Dietitian
Tel: 020 8642 6011 (ext. 1455)

Stool Collection Kit: Contents

1. Copy of the above letter (‘Instructions for collecting your stool sample’)
2. One pair of sterile gloves
3. One wooden spatula
4. One 25cm by 12cm cardboard tray
5. One yellow screw-top sample collection pot
6. One sterile ‘Biochemistry’ specimen bag with sealable strip
7. One white envelope (self-addressed to the Research Dietitian)
8. One pharmacy bag

APPENDIX 4

Statistical Analysis Plan

Statistical Analysis Plan

CCR #:	3142
Version Number:	05
Date (dd/mmm/yy):	09 June 2104
Study protocol Version:	9.0 – 24/01/12
EUDRAC #:	<< >>

A randomised controlled trial to investigate the role of low or high 'fibre' diets in patients undergoing pelvic radiotherapy

The 'Fibre Study'

TABLE OF CONTENTS

LIST OF ABBREVIATIONS / TERMS

Abbreviation or special term	Explanation
AUC	Area under the curve
BMI	Body Mass Index
BMR	Basal Metabolic Rate
BSC	Bristol Stool Chart
CRF	Case Report Form
EBRT	External Beam Radiotherapy
IBDQ	Inflammatory Bowel Disease Questionnaire
IBDQ-B	Inflammatory Bowel Disease Questionnaire – Bowel subset
ICR	Institute of Cancer Research
IMRT	Intensity Modulated Radiotherapy
Nadir (score)	Lowest on treatment score achieved (excluding baseline score)
NSP	Non-starch Polysaccharide
RT	Radiotherapy
SAP	Statistical Analysis Plan
SCFA	Short chain fatty acids
TEI	Total Energy Intake

AMENDMENT HISTORY

Date	Brief description of change
February 2014	Version 1 created for comment by statistician
April 2014	Version 2 created by study PI incorporating comments by PI and statistician
April 2014	Version 3 circulated with comments discussed between statistician and study PI
June 2014	Version 4 created for circulation to study CI and PhD Supervisors
June 2014	Version 5 created to incorporate comments from CI, PI and statistician

1.0 Study Details

1.1 Study objectives

Primary Objective (Acute setting)

- To examine the effect of low, high or habitual (control group) fibre intake on gastrointestinal symptoms, measured using the IBDQ-B in patients receiving radical radiotherapy treatment for pelvic malignancies.

Primary Objective (Late setting)

- To examine the effect of low, high or habitual fibre intake on gastrointestinal symptoms at one year after radical radiotherapy treatment for pelvic malignancies, measured using the IBDQ-B.

Secondary Objectives

- To measure the effect of low, high or habitual fibre intake on Quality-of-Life measured using the IBDQ in patients receiving radical radiotherapy treatment for pelvic malignancies.

- To measure the effect of low, high or habitual fibre intake on stool form and frequency using the Bristol Stool Chart.

- To measure the effect of low, high or habitual fibre intake on the change in faecal short chain fatty acids between week 1 of radiotherapy and end of radiotherapy.

- To assess compliance with fibre prescription (study arms i and ii only) and daily habitual fibre intake measured as non-starch polysaccharides (NSP in grams/day) assessed using Dietplan software.

- To assess changes in nutritional intake and nutritional status between week 1 and end of radiotherapy.

- To measure compliance with fibre prescription using 7-Day Food Diaries at week 1 and end of radiotherapy.

- To assess in the low and high fibre groups the ease of use of the study interventional guidance booklet for enabling patients to estimate their daily intake of NSP using of a study-specific questionnaire

- To assess the variability between investigators in analysis of dietary data using Dietplan by taking a sample of 18 randomly selected end

of radiotherapy 7 Day Food Diaries (i.e. six diaries from each study arm) and examining the difference in the analysis of these diaries between three investigators blinded to arm allocation.

- To examine the relationship between volume of irradiated bowel and onset and severity of gastrointestinal symptoms as measured by the IBDQ-B and the Bristol Stool Chart. This analysis will be done using the ICR/RMH VODKA software platform by Dr Helen McNair (RMH) and Dr Sarah Gulliford (ICR) and will not be described further in this SAP.

- To assess the economic burden of managing symptoms in all patients using the study specific Cost Questionnaire This analysis will be performed by Dr Heather Gage at Surrey University and will not be described further in this SAP.

1.2 Study design

The Fibre Study is a two centre randomised controlled trial in patients undergoing radical or adjuvant radiotherapy to the pelvis. Patients were recruited from The Royal Marsden NHS Foundation Trust (Sutton and London) and from The Royal Surrey County Hospital, Guildford. Patients were randomised into three groups: i) Low fibre; ii) high fibre; and iii) habitual fibre intake 'control' group. All groups received the same standard dietetic intervention (weekly interviews) but in addition the intervention groups (i and ii) received advice and written guidance on how to achieve their prescribed fibre (NSP) intake. At randomisation the groups were stratified by disease site (i.e. gynaecological and gastrointestinal) and by receipt, or not, of concomitant chemotherapy.

All patients were asked to keep a daily record of stool characteristics (stool type and frequency) using the Bristol Stool Chart. Weekly IBDQ and IBDQ-B scores for measurement of QoL and bowel symptom severity respectively were collected weekly. All patients completed a short one page cost questionnaire (weekly) to assess the economic impact of symptom management. Patients in the intervention arms (groups i and ii) completed several additional questions regarding the costs (if any) of adhering to their fibre prescription and the palatability of the intervention diet. Patients in the intervention arms were also asked to keep a fibre exchange diary detailing the number of fibre exchanges (which equate to grams of NSP) consumed each day. A study specific guidance booklet was designed to help patients estimate their daily fibre exchange intake. Ease of use of the booklet was assessed using a study specific questionnaire.

1.3 Number of subjects

This 3-arm study with 90% power and alpha = 0.02 (3-way comparison for multiple testing) was designed to detect a difference of 6 points in the IBDQ-

B score (between baseline and on-treatment nadir) between any of the three arms (standard deviation of 8.35 in IBDQ-B scores using previous data) and required 52 patients per arm (n=156 in total). An additional 21 patients were to be recruited to allow for those who do not complete their radiotherapy or withdrew prematurely from the study making a total of 177 to be randomised. The study was closed to recruitment in December 2013 with 166 patients randomised to the study. Seven patients were withdrawn making a total of 159 patients with data for analysis.

2.0 Analysis Sets

2.1 Definition of analysis sets

All randomised patients with baseline and at least 1 further on-treatment IBDQ-B score will be included in the primary analysis. Patients missing a baseline score will be included if they have a week 2 score and two subsequent on-treatment scores.

2.2 Scope of data to be analysed

The majority of data to be analysed as described in this SAP are contained within the Case Report Form (CRF) for the study (version 6 May 2009). In addition a sub-set of supplementary data has been extracted from patient-reported documents. This data has not been captured on the CRF and thus not entered into the Fibre study database. The reason for this is that the summary data required to be extracted from these patient completed documents has only recently been agreed. Appendix 1 lists these supplementary data items.

It has been agreed with the Head of Statistics that the supplementary data items will be captured within Excel. These items will be added to the downloaded data set extracted from the Trust study database by the Study Statistician and all data will be used for the analyses described in this SAP. All secondary data items will be subjected to a sample 10% accuracy check by the Unit Data Manager prior to analysis. Randomised lists for checking of data will be generated by the Study Statistician. An error rate of >1% for any set of data items will trigger an escalated check which will be determined by the Statistician.

The Head of Statistics has also agreed that the analysis of acute primary and secondary endpoints for the Fibre study can proceed in advance of the one year follow-up data being captured for all recruited patients. The last follow-up measurement will be completed in December 2014.

2.3 Violations and deviations

There are no violations of the study protocol that will exclude patients from the planned analysis. Where there are missing scores for the primary endpoint (IBDQ-B) in the acute setting, missing values will be imputed by averaging the immediately preceding and immediately following scores and imputing the average of these two values.

Since the study is a nutritional interventional study, compliance with prescribed fibre intake will be assessed although non-compliance will not be regarded as a violation. Patients will not be excluded from the analysis described in this SAP for non-compliance (i.e. not meeting their prescribed fibre intake).

An Intention to Treat (ITT) analysis will be performed initially. However, a per-protocol analysis will also be performed. Patients in the interventional groups complying to within 80% of prescribed target fibre intake on the basis of their 7-Day Food Diary for the first week of treatment will be eligible for inclusion in the per protocol analysis.

For Per protocol analysis, compliance will be defined as follows:

a) Low Fibre Group: Achievement to within 80% (defined as a mean daily intake of ≤12.1 grams NSP per day) using 7-Day Food Diary at week one of radiotherapy.

b) High Fibre Group: Achievement to within 80% (defined as a mean daily intake of ≥14.4 grams NSP per day) using 7-Day Food Diary at week one of radiotherapy.

3.0 Primary and Secondary ENDPOINTS

Primary endpoints (Acute setting):

Difference between groups in the mean change in IBDQ-B score between baseline and worst (nadir) score obtained during radiotherapy treatment.

Primary endpoints (Late setting):

Difference between groups in the mean change in IBDQ-B scores between baseline and end-of-radiotherapy ***and*** one year using data only from patients with paired scores to ensure comparability of groups in the acute and late setting.

Secondary endpoints (Acute and Late setting):

Difference between groups in the mean change in IBDQ-B scores between baseline and end of radiotherapy.

Difference between groups in the mean change in IBDQ scores between baseline and worst (nadir) score obtained during radiotherapy treatment.

Difference between groups in the mean change in IBDQ scores between baseline and end of radiotherapy ***and*** one year using data only from patients with paired scores to ensure comparability of groups in the acute and late setting.

Association between the acute IBDQ-B_AUC score and the point score at one year using data from patients in all study groups but only in patients with paired scores in the acute and late setting.

Association between the acute IBDQ_AUC score and the score at one year using data from patients in all study groups but only in patients with paired scores in the acute and late setting.

Comparison of the acute mean IBDQ_AUC and IBDQ-B_AUC by study group.

Difference between study arms between week 1 and end of radiotherapy in the following Bristol Stool Chart measurements: mean stool frequency, mean stool type, number of days on which anti-diarrhoeal medications were used, number of days on which stool form of 6 or 7 was recorded.

Difference between study arms between week 1 and end of radiotherapy in the change in short chain fatty acids including: change in concentration of all fatty acids and change in individual fatty acids.

Difference between study arms in the mean change in daily fibre intake between week 1 and end of radiotherapy.

Difference between study arms in mean change in weight (kgs) from week 1 to end of radiotherapy.

Descriptive analysis of any change in macronutrient or micronutrient nutrient status intake for all groups between week 1 and end of radiotherapy, including differences between groups.

Mean total time delivered per patient by dietitian to manage the intervention with a descriptive comparison of time spent between study arms.

Analysis of between investigator variability in the interpretation of dietary intake data, specifically fibre and total energy intake, as recorded by patients in 7 Day Food Diaries and entered into Dietplan software.

Exploratory endpoints (Acute setting):

The following exploratory endpoints will be described for each arm. Formal statistical comparisons between arms will not be made for these endpoints; instead they will be used to generate hypotheses which may be confirmed by testing in further studies if necessary.

Descriptive comparison of visual analogue scores for the palatability of the study diet (interventional groups I and ii only).

Ease of use of the 'Fibre in Foods' booklet using questionnaire responses obtained from patients in the interventional study arms i and ii only.

4.0 Analysis Methods

4.1 General principles

Data will first be summarised in the groups using descriptive analysis methods for continuous data and will be checked for normality both visually using histograms and formally with Kolmogorov-Smirnov tests. Binary variables will be summarised using counts and percentages.

For comparison of means, provided normality of distribution is demonstrated and homogeneity of variance (Leven's Test) is met, ANOVA techniques will be used in preference to multiple testing methods. This will be followed by an appropriate post-hoc analysis if applicable. A value of $p<0.05$ will be regarded as statistically significant.

If multiple comparisons are used, they will be adjusted using the Bonforroni method. Two sided tests will be used to assess statistically significant differences between the groups. The p value will adjusted in line with the number of comparisons conducted.

All data will be input into the Statistical Package for Social Sciences (SPSS) for statistical analysis. Statistical analysis of the primary endpoints will be conducted by the Study Statistician in collaboration with the Study Principal Investigator.

4.2. Analysis methods

4.2.1 Primary endpoint analysis (Acute setting):

Difference in change in IBDQ-B scores between arms (acute): baseline to nadir

The primary outcome measure is the difference in the change in mean IBDQ-B scores between study arms from baseline to nadir. This will be analysed using ANOVA techniques, provided normality of distribution and homogeneity of variance can be demonstrated. Missing IBDQ-B scores will be replaced by taking the average value of the scores immediately preceding and following the missing score as described in section 2.3.

ANOVA techniques will be used in preference to multiple testing if applicable. An appropriate post-hoc analysis will conducted if a significant difference is observed to establish where these differences occur.

For the acute setting a statistically significant mean difference of 6 or more points between any of the groups will be considered to be a clinically significant difference.

4.2.2 Primary endpoint analysis (Late setting):

Difference in change in IBDQ-B scores between arms (late)

The difference in the change in mean IBDQ-B scores between study arms from baseline to one year will be analysed using ANOVA techniques, provided normality of distribution and homogeneity of variance can be demonstrated. This analysis will only be conducted in patients with paired scores (i.e. scores at baseline and one year) to ensure comparability of groups.

ANOVA techniques will be used in preference to multiple testing if applicable. An appropriate post-hoc analysis will conducted if a significant difference is observed to establish where these differences occur.

For the late setting a statistically significant mean difference of 6 or more points between any of the groups will be considered to be a clinically significant difference.

4.2.3 Secondary endpoints analysis (Acute and Late setting):

Difference in the mean change in IBDQ-B scores between study arms (acute): baseline to end of radiotherapy

Difference between groups in the mean change in IBDQ scores between baseline and worst (nadir) score obtained during radiotherapy treatment.

Difference in the mean change in IBDQ scores between study arms (acute)

The difference in the mean change in IBDQ scores between study arms from baseline to nadir will be analysed using ANOVA techniques provided normality of distribution and homogeneity of variance can be demonstrated. An appropriate post-hoc analysis will conducted if a significant difference is observed to establish where these differences occur.

Difference in the mean change in IBDQ scores between study arms (late)

The difference in the mean change in IBDQ scores by study arm using the acute change in IBDQ between study arms from baseline to end of radiotherapy ***and*** one year using data only from patients with paired scores will be analysed using ANOVA techniques provided normality of distribution and homogeneity of variance can be demonstrated. An appropriate post-hoc analysis will conducted if a significant difference is observed to establish where these differences occur.

Comparison of IBDQ_AUC and IBDQ_B_AUC values between study arms (acute)

The mean IBDQ_AUC and IBDQ-B_AUC values obtained by each study group will be compared using descriptive techniques. Missing values to compute AUC scores will be imputed from the average of the immediately preceding and following scores – see section 2.3.

Association between IBDQ_AUC and IBDQ point score at one year AND IBDQ_B_AUC and IBDQ-B point scores at one year

The IBDQ_AUC and IBDQ-B_AUC values obtained by each patient will be compared with their point IBDQ and IBDQ-B scores at one year using data only from patients with paired values. The intention of this analysis will be to see if there is a correlation between IBDQ _AUC or IBDQ-B_AUC scores and the respective point scores at one year.

Difference in the incidence and severity of toxicity using the BSC data between arms

For each patient, the following continuous variables have been collected: mean weekly stool frequency, mean weekly stool form. Multiple t-tests (independent samples) or ANOVA techniques will be used to compare the difference in means between arms at week 1, week 4 and end-of-radiotherapy weeks.

In addition, for each patient the following categorical variables have been collected: number of days with stool form ≥type 6 and number of days on which anti-diarrhoeal medication was used for week 1, week 4 and end-of-radiotherapy weeks. The Kruskal-Wallis test will be used to compare days with toxicity between arms and number of days use of anti-diarrhoeal medication

Difference in the change in concentration of short chain fatty acids between arms

Difference in the change in concentration of short chain fatty acids (SCFA) between study arms between week 1 and end of radiotherapy will be assessed using the following descriptive techniques:

a) Box whisker plots showing the individual change in SCFA values for each patient presented by study group

b) Line graphs showing the mean change in SCFA values between baseline and end-of-radiotherapy by study group

Difference in NSP (fibre) intake at week 1 and end of radiotherapy between arms

The mean weekly fibre intake (grams / day) in intervention groups i and ii will be compared using ANOVA techniques at week 1 and end of RT weeks. The purpose of these comparisons will be to examine whether significant differences in fibre intake between arms are apparent at week 1 and that these differences are maintained at end of RT.

Difference in the change in body weight between arms

Difference in the mean change in body weight between study arms will be compared using ANOVA techniques from week 1 to end-of-radiotherapy weeks. The purpose of these comparisons will be to ensure that implementation of the study diet has no adverse effect on weight maintenance.

Analysis of compliance

The incidence of compliance versus non-compliance with fibre prescription in study arms i and ii will be reported using descriptive techniques. Compliance is defined as in section 2.3.

Analysis of change in macro-nutrient and micro-nutrient intake

The analysis of the percentage of the diet made up from carbohydrates, protein and fat will be assessed at week 1 and end of RT week using data from 7 Day Food diaries which has been entered into Dietplan for analysis. The results of this analysis will be reported using descriptive techniques. In addition, a similar analysis of micro-nutrients will be conducted.

Time required for intervention

At baseline and weekly during radiotherapy the total time taken for interviewing patients in the study by a dietician will be recorded. These times will be summed to give a total time per patient. These totals will be summarised by arm using descriptive statistics.

Analysis of inter-investigator error in the analysis of 7 Day Food diaries

Inter-observer error between investigators regarding input and interpretation of 7-Day Food Diary records to Dietplan will be assessed using 18 randomly selected end of RT week 7-Day Food Diaries.

ANOVA techniques will be used to assess whether there are significant differences between investigators in each set of diaries analysed by study arm. Investigators will be blinded to the study arms to which the sample of 18 patients have been allocated.

4.2.4 Exploratory endpoints

Palatability of study diet (intervention arms only):

At the end of radiotherapy patients in the interventional arms only were asked to mark on a visual analogue scale (VAS, measured from 0 to 15cm) the palatability of the study diet. VAS scores by arm will be summarised using descriptive statistics.

Analysis of Ease of Use of Fibre in Foods booklet using Questionnaire scores

The returned questionnaires regarding ease of use of the 'Fibre in Foods' booklet will be analysed and reported using descriptive techniques.

5.0 Interim Analyses

The Head of Statistics has agreed that the analysis of acute data can be conducted in advance of the completion of one year follow-up measurements. The last one year post radiotherapy follow-up measurement will be completed in December 2014.

The study Steering Committee has requested that the results of the acute analysis be disseminated amongst the Steering Committee members as soon as they become available. This has been agreed by the study Chief Investigator and the Head of Statistics.

6.0 Changes of Analysis from Protocol

Not applicable

7.0 TIMING OF STATISTICAL ANALYSIS

See above for information regarding the interim analysis. It is anticipated that the full acute analysis of data generated by this study will be completed by June 2014.

8.0 References

Authoring Instructions
Appropriate references are included in the study protocol.

9.0 Appendix 1 – Supplementary data items

List of Data items to be included in the study analysis not captured within the CRF (see text for explanation)

Source (capture) document	**Description of data items**
Bristol Stool Chart	Mean stool frequency - week 1 of RT
	Mean stool frequency - End of RT
	Mean stool frequency by treatment week
	Number of days stool type ≥ 6 - week 1 of RT
	Number of days stool type ≥ 6 - End of RT
	Number of days stool type ≥ 6 by treatment week
	Mean stool type - week 1 of RT
	Mean stool type - End of RT
	Mean stool type by treatment week
	Number of days medication used - week 1 of RT
	Number of days medication used - End of RT
	Number of days medication used by treatment week
Faecal Short Chain Fatty Acids	Total faecal SCFA concentration - week 1 of RT
	Butyrate concentration - week 1 of RT
	Propionate concentration - week 1 of RT
	Acetate concentration - week 1 of RT
	Total faecal SCFA concentration - End of RT
	Butyrate concentration - End of RT

	Propionate concentration - End of RT
	Acetate concentration - End of RT
Fibre Exchange Diary	Mean NSP intake (fibre exchanges) - week 1 of RT
(Study arms i and ii only)	Mean NSP intake (fibre exchanges) - End of RT
	Mean NSP intake (fibre exchanges) by treatment week
Nutritional Data (Dietplan)	Mean NSP intake - week 1 of RT
To include but not limited to:	Mean NSP intake - End of RT
	Total Energy intake (kcals) - week 1 of RT
	Total Energy intake (kcals) - End of RT
	Proportion of diet as carbohydrate - week 1 of RT
	Proportion of diet as carbohydrate - End of RT
	Proportion of diet as protein - week 1 of RT
	Proportion of diet as protein - End of RT
	Proportion of diet as fat - week 1 of RT
	Proportion of diet as fat - End of RT
	TEI (total energy intake) / BMR - week 1 of RT
	TEI (total energy intake) / BMR - End of RT
Study arms i and ii only:	Compliance within 80% of NSP prescription - week 1 of RT
	Compliance within 85% of NSP prescription - week 1 of RT
	Compliance within 90% of NSP prescription - week 1 of RT
	Compliance within 80% of NSP prescription - End of RT
	Compliance within 85% of NSP prescription - End of RT
	Compliance within 90% of NSP prescription - End of RT
Ease of Use of Guidance Tools	Five questions (descriptive analysis only)

Authoring Instructions

This is the final version of the SAP and supersedes all previous versions.

<< >>

APPROVALS:

A randomised controlled trial to investigate the role of low or high 'fibre' diets in patients undergoing pelvic radiotherapy

The 'Fibre Study'

Study Statistician

<<Name>> Date

A randomised controlled trial to investigate the role of low or high 'fibre' diets in patients undergoing pelvic radiotherapy

The 'Fibre Study'

Chief Investigator

<<Name>> Date

APPENDIX 5

Copies of peer reviewed publications

Fiber in the Treatment and Maintenance of Inflammatory Bowel Disease: A Systematic Review of Randomized Controlled Trials

Linda Wedlake, MSc, RD,[*,†] Natalie Slack, MSc, RD,[†] H. Jervoise N. Andreyev, PhD,[‡] and Kevin Whelan, PhD, RD[†]*

Background: Dietary fiber may favorably influence fermentation, gastrointestinal inflammation, and disease progression in Crohn's disease, ulcerative colitis (UC), and pouchitis and offer an attractive therapeutic addition to pharmacological treatment. This systematic review appraised data from randomized controlled trials of fiber in the management of inflammatory bowel disease.

Methods: The review followed Cochrane and PRISMA recommendations. Seven electronic databases were searched along with hand searching and contacting experts. Inclusion criteria were randomized controlled trials of the effects of fiber on clinical endpoints (primarily disease activity for treatment or maintenance) or physiological outcomes in patients with inflammatory bowel disease.

Results: In total, 23 randomized controlled trials fulfilled the inclusion criteria (UC, 10; Crohn's disease, 12; and pouchitis, 1) recruiting 1296 patients. In UC, 3/10 studies reported fiber supplementation to benefit disease outcomes. In Crohn's disease, 0/12 studies and in pouchitis 1/1 study reported a benefit on disease activity. Despite this, a number of studies reported favorable intragroup effects on physiological outcomes including fecal butyrate, fecal calprotectin, inflammatory cytokines, microbiota, and gastrointestinal symptom indices. Meta-analysis was not possible.

Conclusions: There is limited weak evidence for the efficacy of fiber in improving disease outcomes in UC and pouchitis. The potential antiinflammatory role of fiber is intriguing and merits further investigation in adequately powered clinical trials. Excluding overt gastrointestinal obstruction, there was no evidence that fiber intake should be restricted in patients with inflammatory bowel disease.

(Inflamm Bowel Dis 2014;20:576–586)

Key Words: Crohn's disease, ulcerative colitis, pouchitis, fiber, prebiotic, gastrointestinal, inflammatory bowel disease

Approximately 2 million people worldwide are affected by inflammatory bowel disease (IBD), which comprises Crohn's disease (CD), ulcerative colitis (UC), and pouchitis.[1] During active phases of disease, symptoms can have a profound impact on patients' quality of life[2] and include diarrhea and abdominal pain and in CD, in particular, anorexia, and undernutrition.[3]

The pathogenesis of IBD is not entirely understood. It is postulated that it results in part from a mucosal immune response to the commensal gastrointestinal microbiota in genetically susceptible individuals.[4] Although no single pathogen has yet been implicated, the compromised mucosal barrier function in both CD and UC may allow immunogenic luminal bacteria access to the underlying lamina propria, thus perpetuating an on-going inflammatory response.

The aim of clinical management is to induce and maintain remission and prevent disease progression. Pharmacological agents are the mainstay of management,[5] although none are entirely free of side-effects, and patients who become refractory to them may require surgical intervention. Many patients with IBD are interested in dietary approaches to managing symptoms. CD in particular has been shown to be amenable to dietary intervention with enteral formula inducing remission in 60% to 85% of patients.[6]

The efficacy of dietary fiber in managing IBD was first investigated over 30 years ago.[7] The scientific rationale relates to the beneficial effects of fiber on gastrointestinal function[8] and also the production of the fiber metabolites short-chain fatty acids particularly butyrate.[8,9] Because intestinal inflammation is initiated as a consequence of an aberrant response to the commensal microbiota, it follows that dietary substrates that modify these communities or their metabolites or enhance epithelial barrier function[9] may be helpful. Despite the potentially beneficial impact of fiber in reducing inflammation through such mechanisms, many patients with IBD have been advised to reduce fiber consumption.[10,11] A number of trials have investigated the efficacy

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.ibdjournal.org).

Received for publication October 15, 2013; Accepted October 29, 2013.

From the *Department of Nutrition and Dietetics, The Royal Marsden NHS Foundation Trust, London, United Kingdom; †Diabetes and Nutritional Sciences Division, School of Medicine, King's College London, London, United Kingdom; and ‡Gastrointestinal Unit, The Royal Marsden NHS Foundation Trust, London, United Kingdom.

The systematic review was internally funded.

The authors have no conflicts of interest to disclose.

Reprints: Kevin Whelan, PhD, RD, Diabetes and Nutritional Sciences Division, School of Medicine, King's College London, 150 Stamford Street, London SE1 9NH, United Kingdom (e-mail: kevin.whelan@kcl.ac.uk).

DOI 10.1097/01.MIB.0000437984.92565.31

Published online 17 January 2014.

and mechanisms of action of fiber in IBD. However, they vary widely in the nature of the intervention and, to our knowledge, have not been systematically reviewed to assist clinicians in making informed decisions to guide practice. This aim of this systematic review is to identify, appraise, and assimilate the randomized controlled trials (RCT) of dietary fiber in the management of IBD.

METHODS

The review was undertaken in line with the guidelines within the Cochrane Handbook for Systematic Reviews of Interventions[12] and adheres to the relevant criteria of the PRISMA statement (preferred reporting items for systematic reviews and meta-analyses)[13] and with particular reference to guidelines for the reporting of nutritional reviews.[14] The methods used were agreed between the authors in advance and documented in a review protocol.

Studies were identified through electronic database searching, hand searching of conference abstracts, screening of references of key articles, and contacting relevant experts. Online database search strategies were developed in conjunction with a senior information specialist. Electronic searching of the following 7 electronic databases was undertaken: MEDLINE (U.S. National Library of Medicine); EMBASE (Elsevier B.V., The Netherlands); CINAHL (CINAHL Information Systems, United States); CENTRAL (The Cochrane Library, Chichester, United Kingdom); Nutrition and Food Sciences (CAB International, United Kingdom); Web of Science (ISI Thomson Scientific, United Kingdom); and Scopus (Elsevier). The final electronic database search date was done in December 2012. Search limits were applied only to exclude animal studies. Database search terms, timeframes, and host interfaces are detailed in Data, Supplemental Digital Content 1, http://links.lww.com/IBD/A354.

Hand searching for relevant conference abstracts was conducted for 2001–2012. The conference/societies and the name of the publications searched were: Digestive Diseases Week (*Gastroenterology*) and annual conferences of the British Society of Gastroenterology (*Gut*); the American Society for Parenteral and Enteral Nutrition (*J Parent Enteral Nutr*); the European Society for Clinical Nutrition and Metabolism (*Clin Nutr*; *Clin Nutr Supp*, *e-SPEN*); the British Dietetic Association (*J Hum Nutr Diet*); and the British Association for Parenteral and Enteral Nutrition (*Proc Nutr Soc*). Reference lists of relevant reviews and studies were also screened. Experts in "fiber in IBD" (n = 10) and "fiber broadly" (n = 7) were contacted to request published or unpublished studies not otherwise identified.

The research question and inclusion and exclusion criteria were developed using a PICOS structure (patient, intervention, comparators, outcome, and study design). RCT with appropriate comparator arms, reporting the effect of an oral fiber intervention (either increasing or decreasing intake) on clinical outcomes (treatment or maintenance) or physiological outcomes in patients with IBD in either remission or relapse were eligible for inclusion. Primary endpoints were clinical indices that enabled reporting of remission rates, remission duration, response rates, or disease activity (Table 1). Studies using pharmacological fiber supplements, food supplements (e.g., added cereal), or dietary advice (e.g., high-fiber dietary advice) were eligible provided that the stated focus of the intervention was dietary fiber modification. The definition of fiber encompassed either plant cell-wall nonstarch polysaccharide "NSP"[15] or the recent CODEX definition.[16,17] Studies employing solely enteral formulas were not eligible because their efficacy could relate to reasons other than presence or absence of fiber alone.

All retrieved citations (titles and abstracts) were imported into bibliographic software (EndNote v15; Adept Scientific, Letchworth Garden City, United Kingdom), to facilitate review and exclusion of duplicates. Two researchers independently reviewed each reference to assess eligibility. Full articles were obtained for all potentially eligible articles and the inclusion criteria were applied to each. Where full articles contained insufficient information, the corresponding author was contacted (1 article). Non-English titles/abstracts were screened by a native speaker where possible.

Two researchers independently extracted and summarized the data from eligible articles. Disagreements regarding eligibility and data extraction were mediated by a third researcher. Suitability of the data for meta-analysis was evaluated by the research team. Quality scoring was undertaken using the Jadad scale.[18]

RESULTS

Articles

A total of 4232 nonduplicated articles were identified of which 123 articles were potentially eligible. After full review, 23 articles (detailing 23 eligible studies) fulfilled the inclusion criteria (Fig. 1). Ten studies were in patients with UC[19–28] of which 1 was published as an abstract only[21]; 12 were in CD,[29–40] of which 2 were non-English language,[35,40] 2 were abstracts,[30,37] and 1 a letter[38]; and 1 was in pouchitis.[41] Of the 17 experts contacted, 71% responded and 1 additional study was identified.

Patients, Comparators, and Interventions

The 23 studies comprised 1296 patients of which 35% were male (where reported). This included 447 patients with UC (46% remission; 26% active disease; 28% "mixed" disease activity), 829 with CD (56% remission; 23% active; 21% mixed), and 20 with pouchitis, all in remission. The methods used to classify disease activity varied between and within diseases. Where employed (16/23 studies), 10 different indices were used. Use of concomitant medications was reported in 20/23 studies.

Fiber supplements were used in 17 studies[19–30,33–35,38,41] and dietary interventions were used in 6 studies.[31,32,36,37,39,40] All except 1 study[36] investigated the efficacy of increased fiber intake. Double blinding occurred in 10 studies,[20,23–25,29,30,33,34,38,41] and blinding of some or all researchers in an additional 7 studies.[26,28,31,32,36,39,40] Most studies compared fiber with no intervention or placebo. The majority (10/17) of fiber supplement

TABLE 1. Detailed Inclusion and Exclusion Criteria and Data Extracted

PICOS	Inclusion and Exclusion Criteria	Data Extracted
Patient	Adult (inpatients or outpatients) older than 18 years of age with CD, UC, or pouchitis in remission or relapse.	Location, clinical setting, age, gender, number of patients recruited, number of patients evaluated (i.e., those with evaluable data at study end), disease type, disease stage, and/or disease severity.
	Original cohorts only (i.e., excluding previous or abbreviated reports and abstracts of the same patient group) to avoid duplication of patient numbers.	
Intervention	Oral pharmacological fiber supplement, food supplement, or dietary advice to increase or decrease fiber intake were eligible. Fiber interventions were required to meet the acknowledged definitions of fiber,[15–17] and therefore included prebiotic fibers. Synbiotic preparations containing a named prebiotic fiber complying with the cited fiber definitions were also eligible irrespective of probiotic species and strain(s) used.	Fiber source, dose, presentation, and period of administration. Presence of coadministered "standard" medication(s) or supplemental nutritional substances. Compliance with interventional dose (if reported) and method of computing compliance. Genus/species/strain of probiotic if administered in conjunction with synbiotic preparation.
Comparators	Reports including a comparator group of either a placebo, no dietary intervention, an alternative dietary intervention, or a pharmacological intervention were included. Reports comparing different doses of fiber without any other comparator group were excluded.	Patient numbers in the intervention and comparator groups and nature of intervention. Group names standardized to avoid confusion.
Outcomes	Clinical outcomes or endpoints including remission, relapse, mortality, morbidity, medication use, symptoms, and quality of life. Physiological outcomes or endpoints related to gastrointestinal inflammation including histology, inflammatory and immunological markers, microbiota, and metabolic substrates. Presence or absence of adverse events related to interventional substrate.	Values, scores, or counts for remission rates, remission duration, response rates, or disease activity (measured using standardized indices), otherwise all other relevant clinical or physiological outcomes or endpoints at relevant time-points including statistical significance if reported. Comparisons of endpoint data between groups were extracted where possible, but within-group comparisons between baseline and follow-up were extracted where of interest.
Study design	RCT. Open label, wholly or partially blinded or placebo-controlled nutritional interventional studies were eligible. Single or multicenter. English or foreign language. Non-RCTs and uncontrolled trials were excluded.	Type of study design, nature of blinding, active interventional period, and duration of follow-up. Authors and publication details. Abstract or full report. Language of publication.

studies were compared with placebo,[20,23–25,29,30,33,34,38,41] whereas most high-fiber dietary interventions were compared with other dietary interventions (e.g., low fiber), but none were compared with a "sham diet."

In the fiber supplement studies, the intervention periods ranged from 14 days to 24 months. All supplements were soluble fibers (e.g., germinated barley, inulin, oligosaccharide/inulin, and psyllium) in doses ranging from 5 to 30 g/d. Seven studies also used probiotics alongside the fiber supplement.[23,24,27–30,33] In the supplement studies, some reported compliance commonly based on counts of unused sachets, however, none quantified fiber intake from background diet. Of the dietary interventions, the duration ranged from 28 days to 24 months resulting in intakes of between 13 and 46 g/d of fiber (where reported), although none reported the relative contributions of insoluble and soluble fibers. Methods of monitoring dietary compliance and estimating fiber intake varied.

Adverse Events and Study Quality

Serious adverse events were inconsistently reported and where reported were unrelated to intervention. No studies were terminated on safety grounds. Most studies clearly reported patient withdrawals (19/23). Few studies were of high quality with only 17% (4/23) scoring the maximum 5 points, 26% (6/23) 4 points, 22% (5/23) 3 points, 17% (4/23) 2 points, and 17% (4/23) 1 point on the Jadad score.

Efficacy of Fiber: Summary

Fiber supplementation had a positive effect on disease outcomes in 3/10 studies in UC[19,21,26] and in the sole pouchitis study.[41] In contrast, none of the 12 studies in CD showed a benefit with 5/12 studies reporting no effect on disease outcomes[29,30,33,34,38] and 3/12 equivalence[32,36,40] (Table 2). In view of the variation in patient groups, stage of disease (remission and active), interventions, comparators, and the definition and methods of measuring outcomes, meta-analysis of the studies were deemed not possible.

UC (Remission)

Four studies in patients with UC in remission recruited 213 patients (Table 3). Two reported positive results on disease activity. In the large 3-arm RCT, comparing psyllium fiber versus mesalamine versus mesalamine and psyllium fiber[19] continued remission at 12 months was similar across all groups implying

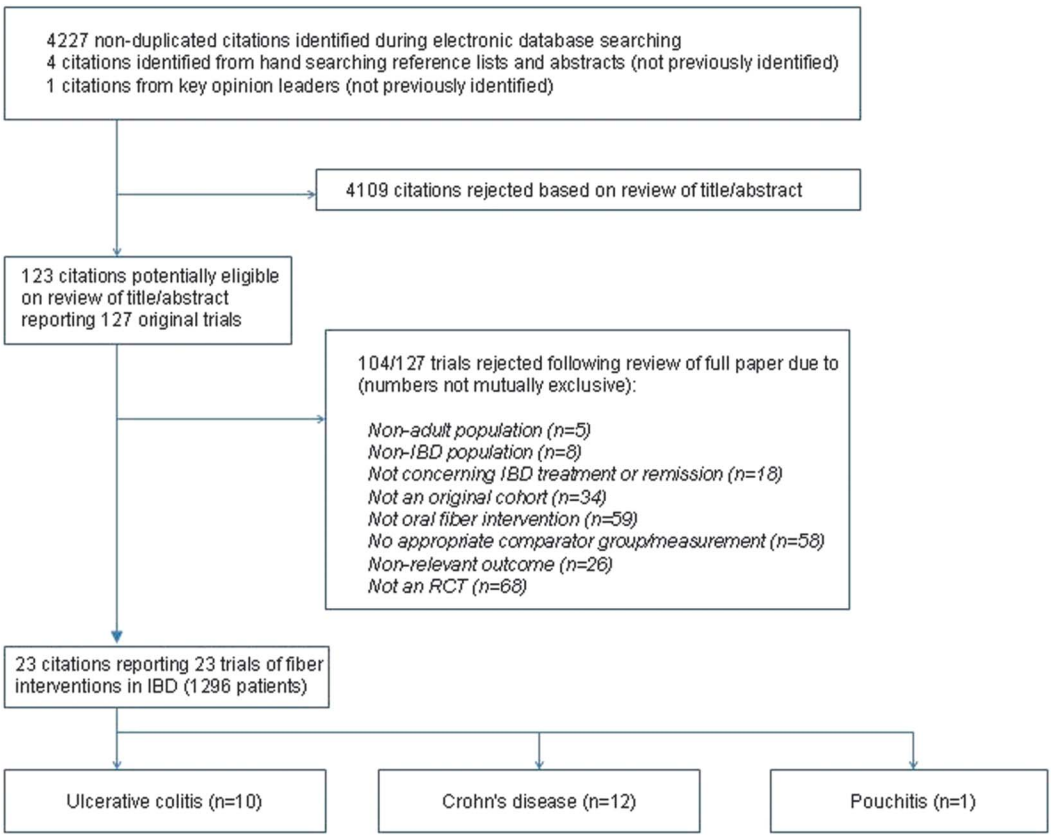


FIGURE 1. Summary of review process and results.

equivalence between fiber and medication, in addition, lower relapse rates were reported in the mesalamine plus psyllium fiber group.[19] Another small RCT reported lower relapse rates at 12 months for psyllium fiber plus mesalamine versus mesalamine alone.[21] Two further studies did not report disease outcomes.[20,22] However, in one study, psyllium fiber resulted in lower gastrointestinal symptom scores at 2 months compared with placebo.[20] In the other study, beneficial effects on proinflammatory blood markers were reported at 2 months.[22]

UC (Active Disease or Mixed Active/Remission)

Five studies in patients with UC with active disease recruited 114 patients (Table 3). One using 20 to 30 g/d of germinated barley fiber reported positive results on disease activity compared with no intervention at 1 month.[26] In 3 other studies, no effect of fiber supplementation on disease outcomes was reported, although positive effects on inflammatory makers were noted. In one study, there was no difference in the numbers achieving remission after 2 weeks between patients receiving prebiotic fibers (oligofructose/inulin) or placebo.[25] However, those receiving prebiotic fibers had significantly lower fecal calprotectin on day 7 but not on day 14 compared with placebo. The same prebiotic fiber was used in another study in combination with a probiotic (synbiotic).[24] The synbiotic did not result in significantly lower disease activity or sigmoidoscopy scores compared with placebo, although it did increase luminal bifidobacteria-specific total rRNA and caused a reduction in epithelial immunological markers compared with baseline values.[24] The largest study reported no benefit on disease activity of a synbiotic supplement at 1 year but noted significantly reduced expression of inflammatory marker myeloperoxidase between groups.[27] One further study (disease outcomes not reported) found that a prebiotic fiber (plus glutamine) caused reduced expression of IL-6 and IL-8 compared with baseline but not to placebo.[23]

One large RCT (n = 120) in a mixed cohort (Table 3) compared psyllium fiber versus probiotic versus psyllium fiber/probiotic. Disease activity was not reported but improved gastrointestinal symptom scores and reduced C-reactive protein occurred at 1 month in the psyllium fiber/probiotic group.[28]

CD (Remission)

Four studies in patients with CD in remission recruited 465 patients. All reported on disease outcomes. Full details of interventions, quality scores, and outcomes are reported in Data, Supplemental Digital Content 2, http://links.lww.com/IBD/A355. One large study (n = 352) reported equivalence with no difference in the number of patients with deteriorating disease at 24 months between those consuming a high (mean intake, 27 g/d) versus low (mean intake, 15 g/d) fiber diet.[32] Two studies investigating a fiber/prebiotic supplement in combination with probiotics

TABLE 2. Summary of Effects of Fiber on Disease Activity (Score, Remission Rates, and Relapse Rates) Compared with Control Group

Study	Disease Stage	Study Aim	Effect on Disease Activity Between Groups (Score, Remission, Relapse Rates)	Summary Effect on Disease Activity
UC				
19	Remission	Maintenance	Equivalent relapse rates to drug treatment	Positive
21	Remission	Maintenance	Reduced relapse rate compared with no fiber	Positive
26	Active	Treatment	Reduced disease activity compared with no intervention	Positive
24	Active	Treatment	No effect on disease activity compared with placebo	No effect
25	Active	Treatment	No effect on disease activity compared with placebo	No effect
27	Active	Treatment	No effect on disease activity compared with no intervention	No effect
20	Remission	Physiological	Disease activity not reported	Not reported
22	Remission	Physiological	Disease activity not reported	Not reported
23	Active	Physiological	Disease activity not reported	Not reported
28	Mixed	Physiological	Disease activity not reported	Not reported
CD				
32	Remission	Maintenance	Equivalent relapse rates compared with low fiber	Equivalence
36	Active	Treatment	Equivalent remission rates compared with low fiber	Equivalence
40	Mixed	Treatment	Equivalent disease activity compared with exclusion diet	Equivalence
29	Remission	Maintenance	No effect on relapse rates compared with placebo	No effect
30	Remission	Maintenance	No effect on relapse times compared with placebo	No effect
33	Active	Treatment	No effect on remission rates compared with placebo	No effect
34	Active	Treatment	No effect on remission rates compared with placebo	No effect
38	Mixed	Treatment	No effect on disease activity compared with placebo	No effect
39	Mixed	Maintenance	No effect on disease activity of low fiber compared with normal diet	No effect
31	Remission	Maintenance	Reduced relapse times in high fiber compared with low fiber	Negative
35	Active	Physiological	Disease activity not reported	Not reported
37	Active	Physiological	Disease activity not reported	Not reported
Pouchitis				
41	Remission	Treatment	Reduced disease activity compared with placebo	Positive

reported no differences in clinical, endoscopic, or physiological outcomes at 24 months[29] or median time to next infusion at 6 months[30] between intervention and placebo groups. One study reported negative outcomes for patients consuming a high-fiber diet with significantly higher treatment failure and shorter time to relapse (1.4 versus 2.8 months) compared with patients on a low-fiber exclusion diet.[31]

CD (Active Disease or Mixed Active/Remission)

Five studies in patients with CD with active disease recruited 193 patients. Disease outcomes were reported in 3 studies. One small study (n = 14) reported equivalence of a high-fiber diet (mean intake 46 g/d) and a low-fiber diet (16 g/d) with a similar proportion of patients achieving remission.[36] Although improved endoscopic appearance was reported in the high-fiber group at 6 weeks, no other differences in physiological or clinical outcomes were observed.

Two further studies using 12 to 15 g/d of prebiotic fiber (oligofructose/inulin) reported no effect on disease outcomes.[33,34] In one study (n = 24 evaluated), no differences in remission rates were reported between groups, although reduced histological and disease activity scores and increased bifidobacteria were noted at 6 months in the prebiotic group compared with baseline.[33] In the other larger RCT (n = 103), no differences between groups were found in clinical or inflammatory markers or selected microbiota at 1 month.[34] However, there were indications of a shift to greater mucosal immunoregulation in the prebiotic group, including significantly higher IL-10 and lower IL-6 positive dendritic cells.[34]

Two further studies did not report on disease activity but noted benefits in other outcomes. In one study, significantly improved gastrointestinal symptom scores after a 28-day high-fiber low refined carbohydrate diet were reported versus those in the nonintervention group, although numbers were small (n = 7).[37] In the other study, significantly improved stool consistency and slower gut transit times were noted in the isphagula-supplemented group compared with no intervention.[35]

Three studies in mixed cohorts (i.e., active disease/remission) recruited 171 patients with all reporting disease outcomes. One reported equivalence in clinical and physiological outcomes at

TABLE 3. RCTs of Fiber Interventions in Adult Patients with UC

	Patient Details					Study Details			Intervention		Outcomes Between and Within Groups	
Reference	Disease	No. of Patients Recruited	No. of Patients Evaluated	Male: Female	Age (Mean), yr	Design	Jadad	Groups	Details by Group	Duration	Clinical	Physiological
Fernandez-Banares et al[19]	Remission UC	105	102	55:47	43	Open label	3	G1: Mesalamine (1.5 g/d) G2: Fiber G3: Fiber + mesalamine	G1: No additional fiber G2: Psyllium (20 g/d) G3: Psyllium (20 g/d)	12 mo	No difference between groups in the probability of continued remission ($P = 0.67$) No difference between groups in treatment effects after adjusting for confounding variables ($P = 0.41$) Lower relapse rates in G3 (23.3%) compared with G1 (37.1%) and G2 (35.1%)	Raised fecal butyrate in G2 patients at 3 months compared with baseline values ($P = 0.018$) ($n = 7$)
Hallert et al[20]	Remission UC	36	29	14:22	43	Cross-over, double blind, placebo	4	G1: Placebo (standard meds) G2: Fiber (standard meds)	G1: Placebo G2: Psyllium (7 g/d)	2 months per group	Reduced severity of total gastrointestinal symptoms in G2 versus G1 ($P < 0.001$) Reduced total number of symptoms in G2 versus G1 ($P < 0.001$)	
Copaci et al[21]	Remission UC	31	31	Gender NR	Age NR	Open label	1	G1: Mesalamine G2: Fiber + mesalamine G3: Probiotic + mesalamine	G1: No additional fiber G2: Psyllium (dose NR) G3: No additional fiber, *S. boulardi*	12 mo	Reduced treatment failure rate (relapse) in G2 (28%) versus G1 (35%) ($P = 0.02$) and G2 versus G3 (30%) ($P = 0.05$) No difference between groups in probability of continued remission ($P =$ NR) Increased number of asymptomatic nights in G2 versus G1 and G3 ($P = 0.001$)	

TABLE 3 (*Continued*)

	Patient Details					Study Details			Intervention		Outcomes Between and Within Groups	
Reference	Disease	No. of Patients Recruited	No. of Patients Evaluated	Male: Female	Age (Mean), yr	Design	Jadad	Groups	Details by Group	Duration	Clinical	Physiological
Faghfoori et al[22]	Remission UC	41	41	26:25	33.5	Open label	1	G1: Control (standard meds) G2: Fiber supplement (standard meds)	G1: No supplement G2: Germinated barley (30 g/d)	2 mo		No differences in TNF-α, IL-6, and IL-8 between G1 and G2 at 2 months, although significant reduction in these in G2 between baseline and 2 mo
Federico et al[23]	Active UC	18	16	9:9	47	Double blind, placebo	4	G1: Placebo (standard meds) G2: Prebiotic fiber/probiotic (standard meds)	G1: Placebo (starch) G2: Oligosaccharide/ inulin (7 g/d), plus *L. paracasei* (5×10^9 cfu), plus added micronutrients	2 mo		Lower serum IL-6 ($P < 0.05$) and IL-8 ($P < 0.01$) in G2 at 2 months compared with baseline values Lower lymphocytic expression of IL-8 ($P < 0.01$) in G2 at 2 months compared with baseline value
Furrie et al[24]	Active UC	18	14	8:8	41.5	Double blind, placebo	5	G1: Placebo (standard meds) G2: Prebiotic fiber/probiotic (standard meds)	G1: Placebo (starch, maltodextrose) G2: Oligofructose/ inulin (12 g/d), plus *B. longum* (2×10^{11} cfu)	1 mo	Reduced sigmoidoscopy scores in G2 versus G1 ($P = 0.06$) No difference between groups in mean clinical disease activity score Bowel frequency improved in G2 versus G1 at 1 mo ($P =$ NR)	Reduced expression of TNF-α and IL-1α in G2 at 1 mo compared with G1 ($P = 0.0177$ and 0.0051, respectively) No difference between groups at 1 mo in the expression of immunological markers, human beta defensins (hBD2, 3, and 4)

TABLE 3 (*Continued*)

Reference	Patient Details: Disease	No. of Patients Recruited	No. of Patients Evaluated	Male: Female	Age (Mean), yr	Study Details: Design	Jadad	Groups	Intervention: Details by Group	Duration	Outcomes Between and Within Groups: Clinical	Physiological
												Lower hBD2, 3, and 4 in G2 at 1 mo compared with baseline values ($P = 0.016$, 0.038, and 0.008) Raised (42-fold increase) in bifidobacterial-specific total rRNA in G2 at 1 mo compared with G1 (4.6-fold increase)
Casellas et al[25]	Active UC	19	15	6:13	36.5	Double blind, placebo	4	G1: Placebo (standard meds) G2: Prebiotic fiber (standard meds)	G1: Placebo (maltodextrin) G2: Oligofructose/ inulin (12 g/d)	14 d	No difference between groups in change in disease activity scores All patients in G2 in clinical remission at 14 days (7/7) compared with 75% (6/8) patients in G1 ($P = 0.155$) Lower disease activity scores in both groups compared with baseline ($P < 0.05$)	Reduced fecal calprotectin in G2 versus G1 at 7 days ($P < 0.05$) but not at 14 days Lower fecal calprotectin in G2 at 7 and 14 days compared with baseline values ($P < 0.05$) No difference between groups in change in inflammatory mediators (IL-6 and PGE-2) or fecal DNA
Kanauchi et al[26]	Active UC	18	18	Gender NR	37.05	Open label	3	G1: Control (standard meds) G2: Fiber (standard meds)	G1: No additional fiber G2: Germinated barley (20–30 g/d)	1 mo	Reduced disease activity score in G2 versus G1 at 1 m ($P = 0.045$)	No difference between groups in the change in serum C-reactive protein concentrations between baseline and 1 mo

TABLE 3 (*Continued*)

Reference	Patient Details				Study Details			Intervention		Outcomes Between and Within Groups	
	Disease	No. of Patients Recruited	No. of Patients Evaluated	Male: Female	Age (Mean), yr	Design	Jadad	Groups	Details by Group	Duration	Clinical	Physiological
Ishikawa et al[27]	Active UC	41	39	24:17	45.5	Open label	2	G1: Control (standard meds) G2: Probiotic, prebiotic fiber (standard meds)	G1: No supplement G2: *B. breve* (3×9^9 cfu), Galact-oligosaccharides (5 g/d)	1 yr	No difference in endoscopic score between G1 and G2, but lower scores between baseline and 1 yr in G2	Lower myeloperoxidase at 1 yr in G2 compared with G1 ($P < 0.05$)
Fujimori et al[28]	Mixed UC (remission, mildly active)	120	94	39:55	36	Open label	3	G1: Probiotic (standard meds) G2: Fiber (standard meds) G3: Probiotic, fiber (standard meds)	G1: *B. longum* (2×1 mo 9^9 cfu) G2: Psyllium (8 g/d) G3: Psyllium, *B. longum*		Improved IBDQ scores at 1 m in G3 ($P = 0.03$) but not in G1 or G2 compared with baseline value	Decrease in C-reactive protein in G3 at 1 month ($P < 0.05$) compared with baseline value

NR, not reported.

1 year between patients consuming a high-fiber diet compared with those on an exclusion diet.[40] Two further studies reported no effect of increased supplemental[38] or dietary fiber.[39] In the dietary fiber study, a fiber-restricted diet (mean intake 3 g/d) resulted in no difference in clinical outcomes at 29 months compared with habitual diet (mean intake 13 g/d).[39] More recently supplementation with the prebiotic fiber (oligofructose/inulin) resulted in no difference in disease activity compared with placebo at 4 weeks, although significant increases in *Bifidobacteria longum* were reported in the prebiotic fiber group compared with baseline values.[38]

Pouchitis

A single cross-over, double-blind, placebo-controlled RCT[41] of 20 patients with pouchitis in remission has reported a positive result and is reported in Data, Supplemental Digital Content 3, http://links.lww.com/IBD/A356. Significantly lower disease activity and higher butyrate concentrations were reported during fiber supplementation (inulin-enriched oral supplement for 3 weeks). No differences were reported in bifidobacteria and lactobacilli, however, there was a reduction in *Bacteroides fragilis*, some strains of which are enterotoxigenic and induce colitis.[42]

DISCUSSION

Dietary fiber has physiological properties that may impact on gastrointestinal inflammation, and it may therefore be efficacious in the management of IBD. This systematic review has identified appraised and assimilated the data from 23 RCTs of dietary fiber in the treatment or maintenance of UC, CD, and pouchitis to assist clinicians in making informed decisions to guide practice. The studies recruited patients in varying disease stages (remission, active, and mixed) used a variety of supplements (germinated barley, inulin, oligosaccharide/inulin mix, and psyllium) or dietary advice (high fiber and low fiber) over a range of differing time periods (2 weeks to 29 months) and recorded a variety of clinical outcomes (remission rates, remission duration, response rates, and disease activity) using varying indices in view of which a meta-analysis was not possible.

Of the 17 fiber supplement studies, few reported positive effects on the primary clinical endpoints (disease activity, remission, and response). Three supplement studies reported some positive effects in UC,[19,21,26] although interestingly these scored low on the Jadad quality score (scores ranged, 1–3). One further high quality study (Jadad score 4) reported that inulin lowered disease activity during remission of pouchitis.[41] Of the remaining 13 supplement studies, 8 found no difference in hard endpoints of disease activity between groups,[24,25,27,29,30,33,34,38] although many showed reductions in disease activity within the fiber groups. In contrast, the 6 dietary intervention studies were all conducted in patients with CD.[31,32,36,37,39,40] Of those that reported on disease activity, none reported significant benefit of high versus low-fiber diets[32,36,37,39,40] with one showing negative results for high-fiber diet compared with low.[31]

Despite limited evidence of efficacy, the benefits of fiber were more commonly seen for supplements rather than dietary

interventions and for the management of UC. All 4 of the studies demonstrating clinical effectiveness, used fiber supplement interventions,[19,21,26,41] and this may be the case for a number of reasons. First, there were many more fiber supplement studies than dietary intervention studies (17 versus 6, respectively). Second, in general, fiber supplement studies were more robustly designed, receiving higher Jadad scores than dietary intervention studies. For example, they were generally larger, thus reducing the risk of a type 2 error and more frequently used placebos, perhaps because of the complexity of using placebo "sham diets" in dietary intervention studies. Third, supplements and dietary advice are very different interventions, the former usually consist of a single fiber with known fermentative properties and the latter would vary between individuals, resulting in varying intakes of different fiber components depending on the patients' food choice. Fourth, it is likely that for many patients, fiber supplements are an easier approach to achieve a high-fiber intake than modifying dietary intake. Compliance with dietary advice is a complex process that requires patients to understand the information (influenced by the skills of the health professional or researcher), to value it (influenced by their health psychology), and then have the ability to adopt it (influenced by their food access, food knowledge, etc). Unfortunately compliance was not robustly measured in many of the dietary intervention trials. Therefore, the extent to which the lack of success of the dietary intervention studies was because of poorer study design, the failure to achieve the dietary fiber target or a true lack of impact of fiber from dietary sources to manage IBD is unclear.

Three studies in UC showed positive between group effects of fiber on disease activity. No studies showed a positive effect in CD, although 3 studies showed equivalent effects of a high-fiber diet compared with another dietary intervention in active,[36] inactive,[32] or mixed disease stage cohorts[40] CD. Importantly, many of the other studies showed significant improvements in other clinical outcomes (e.g., gastrointestinal symptoms) or physiological outcomes (e.g., microbiota and short-chain fatty acid) between groups. Many also showed improvements in disease activity between baseline and endpoint values within the fiber group alone However, as these effects were from RCT, they were not considered indicative of evidence of efficacy in this systematic review. However, details of the most relevant between group and within-group effects have been described in the data tables in order that clinicians and researchers can examine the evidence for specific interventions.

This systematic review has shown that, in general, UC was more amenable to therapeutic fiber interventions than CD. The superior efficacy of fiber in patients with UC may be linked to the formation of its fermentation products, short-chain fatty acids, and, in particular, butyrate in the colon at the site of the disease. Approximately 26% of patients with CD have inflammation regionalized only to the small intestine with another 43% having both small and large intestinal inflammation.[43] Therefore, in the majority of patients with CD, inflammation occurs, at least in part, proximal to the site of fiber fermentation. Two studies have reported increased fecal or colonic butyrate[19,41] in the high-fiber group, 1 in UC[19] and 1 in pouchitis.[41]

Although prebiotic fibers might be expected to offer an additional advantage, the evidence of this review does not support this. Oligofructose and inulin are prebiotic fibers that promote the growth of key components of the gastrointestinal microbiota. Although no studies provided statistically significant evidence for the efficacy of prebiotic fibers, 3 studies reported beneficial trends in immunological markers and selected species.[33,34,38]

Six trials (UC = 4; CD = 2) were identified but excluded on the basis of their nonrandomized, albeit controlled, study designs.[7,10,11,44–46] One in UC reported significantly raised fecal butyrate in the high-fiber diet-treated group versus baseline values.[44] Another reported significantly reduced number of hospital admissions and length of stay in patients with active disease placed on a high-fiber diet for 1 year versus the nondiet group.[11] In contrast, one reported reduced likelihood of continued remission with a high-fiber diet versus sulphasalazine.[7]

In summary, this review has demonstrated the potential for the efficacy of fiber in IBD. There is limited, weak evidence of the effectiveness of isphagula in maintenance of remission of UC, germinated barley in active UC, and inulin in the maintenance of remission in pouchitis. Many within-group effects were observed and given the paucity of high-quality studies, these within group observations merit further exploration in adequately powered and controlled clinical trials. Future studies should consider measurement of physiological outcomes to further elucidate fiber's mechanism of action, taking into account the possible confounding effect of medication. It is recommended that in patients with IBD without overt risk of obstruction, the restriction of dietary fiber is unnecessary, but all patients should be appropriately monitored regarding their tolerance to fiber intake.

ACKNOWLEDGMENTS

The authors thank Ms. Angela McGrath (Senior Information Specialist, King's College London) for advice regarding developing the database search and the numerous experts and report authors who responded to requests for further information. The authors would also like to thank Dr. Charlotte Hedin, Filomena Gomes and Mina Yamazaki Price (King's College London) and Kjell Pennert (Royal Marsden NHS Foundation Trust) for assistance with translation of foreign language articles.

Author contributions: K. Whelan and H. J. N. Andreyev conceived the idea. K. Whelan and L. Wedlake designed the review processes. N. Slack and L. Wedlake designed the electronic search strategies, undertook electronic searching, screened citations, selected articles for inclusion, extracted data, contacted experts, and interpreted the findings. K. Whelan mediated disagreement between authors regarding study inclusion. L. Wedlake and K. Whelan wrote the manuscript and all authors approved the final version.

REFERENCES

1. Loftus EV Jr. Clinical epidemiology of inflammatory bowel disease: incidence, prevalence and environmental influences. *Gastroenterology*. 2004; 126:1504–1517.
2. Bernklev T, Jahnsen J, Lygren I, et al. Health-related quality of life in patients with inflammatory bowel disease measured with the short form-36: psychometric assessments and a comparison with general population norms. *Inflamm Bowel Dis.* 2005;11:909–918.
3. Gerasimidis K, McGrogan P, Edwards CA. The aetiology and impact of malnutrition in paediatric inflammatory bowel disease. *J Hum Nutr Diet.* 2011;24:313–326.
4. Abraham C, Medzhitov R. Interactions between the host innate immune system and microbes in inflammatory bowel disease. *Gastroenterology*. 2011;140:1729–1737.
5. Talley NJ, Abreu MT, Achkar JP, et al. An evidence-based systematic review on medical therapies for inflammatory bowel disease. *Am J Gastroenterol.* 2011;106:S2–S25.
6. Zachos M, Tondeur M, Griffiths AM. Enteral nutritional therapy for induction of remission in Crohn's disease. *Cochrane Database Syst Rev.* 2007;CD000542.
7. Davies PS, Rhodes J. Maintenance of remission in ulcerative colitis with sulphasalazine or a high-fibre diet: a clinical trial. *Br Med J.* 1978;1: 1524–1525.
8. Eswaran S, Muir J, Chey WD. Fiber and functional gastrointestinal disorders. *Am J Gastroenterol.* 2013;108:718–727.
9. Gassull MA. Review article: the intestinal lumen as a therapeutic target in inflammatory bowel disease. *Aliment Pharmacol Ther.* 2006;24(suppl 3): 90–95.
10. Woolner JT, Parker TJ, Kirby GA, et al. The development and evaluation of a diet for maintaining remission in Crohn's disease. *J Hum Nutr Diet.* 1998;11:1–11.
11. Heaton KW, Thornton JR, Emmett PM. Treatment of Crohn's disease with an unrefined-carbohydrate, fibre-rich diet. *Br Med J.* 1979;2:764–766.
12. Higgins JPT, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.1 (Updated September 2008)*. Chichester, United Kingdom: Cochrane Collaboration; 2008.
13. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Ann Intern Med.* 2009;151:W65–W94.
14. Moher D, Tricco AC. Issues related to the conduct of systematic reviews: a focus on the nutrition field. *Am J Clin Nutr.* 2008;88:1191–1199.
15. Department of Health. *Report on Health and Social Subjects No. 41. Chapter 4 Non-starch Polysaccharides in Dietary Reference Values for Food Energy and Nutrients for the United Kingdom*. London, United Kingdom: HMSO; 1991.
16. Cummings JH, Mann JI, Nishida C, et al. Dietary fibre: an agreed definition. *Lancet.* 2009;373:365–366.
17. Mann JI, Cummings JH. Possible implications for health of the different definitions of dietary fibre. *Nutr Metab Cardiovasc Dis.* 2009;19:226–229.
18. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomised clinical trials: is blinding necessary? *Control Clin Trials.* 1996;17:1–12.
19. Fernandez-Banares F, Hinojosa J, Sanchez-Lombrana JL, et al. Randomized clinical trial of Plantago ovata seeds (dietary fiber) as compared with mesalamine in maintaining remission in ulcerative colitis. Spanish Group for the Study of Crohn's Disease and Ulcerative Colitis (GETECCU). *Am J Gastroenterol.* 1999;94:427–433.
20. Hallert C, Kaldma M, Petersson BG. Ispaghula husk may relieve gastrointestinal symptoms in ulcerative colitis in remission. *Scand J Gastroenterol.* 1991;26:747–750.
21. Copaci I, Chira C, Rovinaru I, et al. Maintenance of remission of ulcerative colitis (UC): mesalamine, dietary fiber, S. boulardi. *Dig Liver Dis.* 2000;32(suppl 1):A2.
22. Faghfoori Z, Navai L, Shakerhosseini R, et al. Effects of an oral supplementation of germinated barley foodstuff on serum tumour necrosis factor-α, interleukin-6 and -8 in patients with ulcerative colitis. *Ann Clin Biochem.* 2011;48:233–237.
23. Federico A, Tuccillo C, Grossi E, et al. The effect of a new symbiotic formulation on plasma levels and peripheral blood mononuclear cell expression of some pro-inflammatory cytokines in patients with ulcerative colitis: a pilot study. *Eur Rev Med Pharmacol Sci.* 2009;13:285–293.
24. Furrie E, Macfarlane S, Kennedy A, et al. Synbiotic therapy (*Bifidobacterium longum*/Synergy 1) initiates resolution of inflammation in patients with active ulcerative colitis: a randomised controlled pilot trial. *Gut.* 2005;54:242–249.
25. Casellas F, Borruel N, Torrejon A, et al. Oral oligofructose-enriched inulin supplementation in acute ulcerative colitis is well tolerated and associated with lowered fecal calprotectin. *Aliment Pharmacol Ther.* 2007;25:1061–1067.
26. Kanauchi O, Suga T, Tochihara M, et al. Treatment of ulcerative colitis by feeding with germinated barley foodstuff: first report of a multicenter open control trial. *J Gastroenterol.* 2002;37(suppl 14):67–72.
27. Ishikawa H, Matsumoto S, Ohashi Y, et al. Beneficial effects of probiotic Bifidobacterium and galacto-oligosaccharide in patients with ulcerative colitis: a randomised controlled study. *Digestion*. 2011;84:128–133.
28. Fujimori S, Gudis K, Mitsui K, et al. A randomised controlled trial on the efficacy of synbiotic versus probiotic or prebiotic treatment to improve the quality of life in patients with ulcerative colitis. *Nutrition*. 2009;25:520–525.
29. Chermesh I, Tamir A, Reshef R, et al. Failure of Synbiotic 2000 to prevent postoperative recurrence of Crohn's disease. *Dig Dis Sci.* 2007;52:385–389.
30. Rutgeerts P, D'Haens G, Baert F, et al. Randomized placebo controlled trial of pro- and prebiotics (synbiotics cocktail) for maintenance of infliximab induced remission of luminal Crohn's disease (CD). *Gastroenterology*. 2004;126:A467.
31. Jones VA, Dickinson RJ, Workman A, et al. Crohn's disease: maintenance of remission by diet. *Lancet*. 1985;2:177–180.
32. Ritchie JK, Wadsworth J, Lennard-Jones JE, et al. Controlled multicentre therapeutic trial of an unrefined carbohydrate, fibre rich diet in Crohn's disease. *Br Med J (Clin Res Ed).* 1987;295:517–520.
33. Steed H, Macfarlane GT, Blackett KL, et al. Clinical trial: the microbiological and immunological effects of synbiotic consumption—a randomized double-blind placebo-controlled study in active Crohn's disease. *Aliment Pharmacol Ther.* 2010;32:872–883.
34. Benjamin JL, Hedin CRH, Koutsoumpas A, et al. Randomised, double-blind, placebo-controlled trial of fructo-oligosaccharides in active Crohn's disease. *Gut*. 2011;60:923–929.
35. Koch H. Adjuvant treatment of Crohn's disease with a Psyllium preparation [in German]. *Therapiewoche*. 1984;34:4545–4548.
36. Bartel G, Weiss I, Turetschek K, et al. Ingested matter affects intestinal lesions in Crohn's disease. *Inflamm Bowel Dis.* 2008;14:374–382.
37. Brotherton CS, Taylor AG, Anderson JG. Can a high fiber diet improve bowel function and health-related quality of life in patients with Crohn's disease? *FASEB J.* 2012;26:1b338.
38. Joossens M, De Preter V, Ballet V, et al. Effect of oligofructose-enriched inulin (OF-IN) on bacterial composition and disease activity of patinets with Crohn's disease: results from a double-blinded randomised controlled trial. *Gut*. 2012;61:958.
39. Levenstein S, Pranter C, Luzi C, et al. Low residue or normal diet in Crohn's disease: a prospective controlled study in Italian patients. *Gut*. 1985;26:989–993.
40. Stange EF, Schmid U, Fleig WE, et al. Exclusion diet in Crohn's disease: a controlled, randomised study [in German]. *Z Gastroenterol.* 1990;28:561–564.
41. Welters CFM, Heineman E, Thunnissen FBJM, et al. Effect of dietary inulin supplementation on inflammation of pouch mucosa in patients with an ileal pouch-anal anastomosis. *Dis Colon Rectum.* 2002;45:621–627.
42. Sears CL. Enterotoxigenic *Bacteriodes fragilis*: a rogue among symbiotics. *Clin Microbiol Rev.* 2009;22:349–369.
43. Freeman HJ. Application of the Montreal classification for Crohn's disease to a single clinician database of 1015 patients. *Can J Gastroenterol.* 2007;21:363–366.
44. Hallert C, Bjorck I, Nyman M, et al. Increasing faecal butyrate in ulcerative colitis patients by diet: controlled pilot study. *Inflamm Bowel Dis.* 2003;9:116–121.
45. Hanai H, Kanauchi O, Mitsuyama K, et al. Germinated barley foodstuff prolongs remission in patients with ulcerative colitis. *Int J Mol Med.* 2004; 13:643–647.
46. Van Loo J, Bosscher D, Franck A, et al. On the use of prebiotic food ingredient Synergy1 (Oligofructose enriched inulin) in the management of inflammatory bowel disease. *FASEB J.* 2006;20: A989.

AP&T Alimentary Pharmacology and Therapeutics

Systematic review: the efficacy of nutritional interventions to counteract acute gastrointestinal toxicity during therapeutic pelvic radiotherapy

L. J. Wedlake*, C. Shaw*, K. Whelan† & H. J. N. Andreyev‡

*Department of Nutrition and Dietetics, The Royal Marsden NHS Foundation Trust, Sutton & London, UK.
†King's College London, School of Medicine, Diabetes and Nutritional Sciences Division, London, UK.
‡The GI Unit, The Royal Marsden NHS Foundation Trust, London, UK.

Correspondence to:
Dr H. J. N. Andreyev, The GI Unit, Department of Medicine, Royal Marsden Hospital, Fulham Road, London SW3 6JJ, UK.
E-mail: J@andreyev.demon.co.uk

Publication data
Submitted 18 October 2012
First decision 5 November 2012
Resubmitted 12 March 2012
Accepted 28 April 2013
EV Pub Online 23 April 2013

This uncommissioned systematic review was subject to full peer-review.

SUMMARY

Background
Radiotherapy-induced damage to noncancerous gastrointestinal mucosa has effects on secretory and absorptive functions and can interfere with normal gastrointestinal physiology. Nutrient absorption and digestion may be compromised. Dietary manipulation is an attractive option for the prevention and management of symptoms.

Aim
To synthesise the evidence for the use of elemental formula low- or modified-fat diets, fibre, lactose restriction and probiotics, prebiotics and synbiotics to protect the gastrointestinal tract during pelvic radiotherapy.

Methods
Four electronic databases were searched. Randomised controlled trials (RCT), controlled trials (CT) and case series in adult patients receiving radiotherapy for pelvic cancers employing nutritional interventions to reduce gastrointestinal toxicity were included. Methodological quality was assessed using a bespoke tool.

Results
Twenty-two original studies (2446 patients) were identified. Study quality was highly variable with only 37% scoring $\geq$10 points (maximum 17: bespoke scale). Few studies assessed compliance with the intervention. End-points varied and included symptom scales (IBDQ, CTC, Bristol Stool and RTOG). Evidence from RCTs was weak for elemental, low- or modified-fat, fibre and low-lactose interventions with 1/4, 3/4, 1/2, 0/1 trials respectively reporting favourable outcomes. Evidence for probiotics as prophylactic interventions was more promising (4/5 favourable), but dose, strains and methodologies varied.

Conclusions
There is insufficient high-grade evidence to recommend nutritional intervention during pelvic radiotherapy. Total replacement of diet with elemental formula may be appropriate in severe toxicity. Probiotics offer promise, but cannot be introduced into clinical practice without rigorous safety analysis, not least in immunocompromised patients. The methodological quality of nutritional intervention studies needs to be improved.

Aliment Pharmacol Ther 2013; **37:** 1046–1056

doi:10.1111/apt.12316

INTRODUCTION

Radiotherapy-induced gastrointestinal toxicity: the scale of the problem

Therapeutic irradiation ('radiotherapy') is now firmly established as a cornerstone of modern cancer treatment with an estimated half of all newly diagnosed cancer patients receiving radiotherapy at some point in the course of their disease.[1] Pelvic radiotherapy for gynaecological, urological and lower gastrointestinal malignancies, as sole therapy or in combination with surgery and chemotherapy, is used to treat an estimated 300 000 patients annually in the United States and Western Europe. However, despite recent advances in the planning and delivery of radiotherapy, treatment-induced toxicity of noncancerous tissues remains dose-limiting.

During fractionated pelvic radiotherapy, delivered daily over treatment periods of 5–7 weeks, up to 90% of patients experience symptoms of varying severity due to the close proximity of the gastrointestinal tract to the pelvic organs.[2] Symptoms experienced during treatment include change in bowel habit (94%), loose stool (80%), bowel frequency (74%), urgency (39%) and faecal incontinence (37%).[2] Once radiotherapy ceases, gastrointestinal symptoms continue to emerge and 50% of patients describe them as having a detrimental effect on their quality of life.[3–9]

Mechanisms of normal tissue damage

Current opinion regarding the pathophysiology of tissue damage is that the radio-therapeutic injury is similar to a complex wound in organised tissues, which importantly includes many interacting and mutually dependent cellular lineages together with biologically active extracellular molecules.[10] Radiotherapy-induced (free radical) damage to cellular DNA affects any number of cells within these organised structures and delivers a series of fractionated repeated insults, contributing to accumulating direct tissue injury and inflammatory cell recruitment. The process of wound healing is therefore constantly interrupted, resulting in the composition of affected noncancerous 'normal tissue' at the end of a prolonged course of treatment being quite different from that which existed before treatment commenced.[10]

Studies investigating changes in the morphology of the rectal wall in patients during the acute phase of treatment[11, 12] have revealed an inflammatory process in the mucosa that is maximal at 2 weeks after radiotherapy commences, but in which reparative processes are evident at 6 weeks despite worsening symptoms. Some of these early lesions may resolve, but changes consistent with chronic ischaemia and fibrosis can emerge months or years later, resulting in functional impairment to normal gastrointestinal physiology and a spectrum of clinical outcomes recently defined as 'pelvic radiation disease'.[13]

Radiotherapy-induced gastrointestinal tract toxicity

Mucosal biopsies from superficial layers of irradiated rectal wall[11, 12] have revealed changes, which, if common to both the small and large intestines, could affect absorptive and secretory functions. These include atrophy of surface epithelium, acute inflammation of the crypts, inflammatory cell infiltration of surface epithelium, accumulation of eosinophilic granulocytes,[11] flattening of columnar cells, loss of goblet cells, oedema[11] and excessive collagen deposition.[12] The damaging effects of pancreatic enzymes and bile acids given this scenario has been well characterised in preclinical models.[14–20] Attendant nutrition-related problems include disaccharidase malabsorption (notably lactose, fructose[21–23] and possibly sucrose), bile acid malabsorption,[24, 25] fat malabsorption, dysmotility[26, 27] and small intestinal bacterial overgrowth.[23] Whilst all of these disorders result from specific aberrations in gastrointestinal functionality, they often have the same clinical end-point, gastrointestinal disturbance, malabsorption and abnormal stool output.

Potential role of dietary modulation

It is becoming increasingly clear that late radiotherapy-induced toxicity has a 'consequential' component,[28, 29] independent of dose and fractionation. The evidence to support this includes the finding that cumulative acute, sustained mild or moderate toxicity appears to be a better predictor of chronic morbidity than a single acute severe peak.[30] Therefore, strategies including dietary manipulation to limit the acute inflammatory processes should protect against the subsequent self-perpetuating fibrotic processes. This article aims to provide a comprehensive review of the potential benefit of nutritional manipulation during radical pelvic radiotherapy.

METHODS

For this review, on-line databases PUBMED, MEDLINE, EMBASE and the Cochrane library were searched from 1966 to March 2012 using the following terms: 'pelvic radiotherapy', 'nutrition', 'radiation enteritis', 'radiation-induced bowel damage', 'diarrhoea', 'bowel symptoms', 'nutrition', 'dietary intervention', 'elemental', 'reduced fat', 'lactose', 'probiotic, 'synbiotic', 'fibre', 'non-starch

polysaccharide', 'psyllium', 'ispaghula', 'plantago ovata' to retrieve potentially relevant articles. Animal and non-adult studies were excluded. Retrieved articles were reviewed for relevance, duplicates discarded and the full text of all potentially relevant articles retrieved and assessed for inclusion using predetermined criteria. Reference lists of all included articles were reviewed for additional possibly relevant citations.

Randomised controlled trials (RCT), controlled trials (CT) and case series recruiting adult patients, receiving radical daily radiotherapy for pelvic malignancies, employing nutritional interventions and reporting outcomes related to gastrointestinal symptoms or treatment-induced toxicity have been included. Studies investigating more than one nutritional intervention are described with respect to the primary intervention.

The methodological quality of trials was assessed with reference to quality criteria from published sources.[31, 32] A tabulation detailing the extent to which each study met each criteria and a quality score based on the number of unequivocal 'yes' responses is provided as an online supplementary file. A summary of inter-group effects (RCT only) is included detailing 'improved', 'no difference' or 'worse' outcomes vs. comparator group(s).

Two previous reviews have been published.[33, 34] One covers the period 1966–2003 and in contrast to the current review, includes studies addressing malnutrition, but does not cover prebiotic or synbiotic interventions.[33] A more recent meta-analysis has examined the efficacy of probiotic interventions (only) up to January 2009.[34] The current review extends the scope of both of these previous reviews to 2012, but does not include studies addressing malnutrition.

RESULTS

Twenty-four papers[21, 22, 25, 35–55] describing 22 original studies, recruiting 2446 patients, satisfied the inclusion criteria. The studies include 16 RCT,[21, 25, 35–38, 41–43, 45, 48–53] two nonrandomised CT[39, 40] and four case series.[22, 44, 46, 47] All studies were published in English language and two were published as abstracts only (Table S1).[36, 41] In total, these studies comprised six elemental formula interventions (836 patients),[35–40] four low- or modified-fat dietary interventions (316 patients),[21, 25, 41, 42] four high- or low-fibre interventions (275 patients),[43–46] three lactose interventions (275 patients)[22, 47, 48] and five probiotic interventions (901 patients).[49–53] A quality analysis is given in Table S2. This indicates that only six studies scored ≥ 10 points of a maximum 17 points. A summary of inter-group effects (RCT only) is given in Table 1. Using only inter-group outcomes, 9/16 studies reported favourable outcomes for the intervention whilst 7/16 showed no difference or worse outcomes. Evidence for the efficacy of each intervention is presented below together with the rationale for the intervention and a brief concluding statement.

Elemental formula

Rational. Elemental nutritional formulas provides essential macronutrients in readily digestible form with protein supplied as amino-acids or peptides, fats primarily as medium chain triglycerides (MCT) and carbohydrates largely as maltodextrins. In appropriate volume, these formulae contain all essential macronutrients and micronutrients and can be used as a sole source of nutrition for prolonged periods. The rationale for their use during radiotherapy is twofold: first, the provision of nutrients that can be readily absorbed by the gastrointestinal mucosa and secondly, their potential to reduce pancreatic and biliary secretions that may aggravate pre-existing mucosal inflammation. Delivery of elemental formula to the mid-distal and distal jejunum can suppress pancreatic secretions,[56, 57] whilst delivery of elemental formula to the proximal duodenum suppresses maximal mean postprandial pancreatic secretions by up to 50%, compared to polymeric formula, in healthy human volunteers.[58]

Evidence. Six studies, four RCT[35–38] and two CT[39, 40], have recruited 836 patients. One study[38] is an analysis of a sub-group of patients recruited to a larger RCT.[35] All studies were preventative in aim with elemental formulas providing between 33% and 100% of daily caloric needs. Two studies used elemental formula as the sole nutritional intervention;[37, 40] the remaining studies advised patients to additionally follow a low-fibre diet[35, 38] a low-fibre, lactose-restricted, low-fat diet[39] or a natural diet (not defined).[36] All studies (except one[40]) used an interventional period of between 3 and 6 weeks coincident with radiotherapy treatment. The largest study ($n = 677$) reported a significant reduction in the proportion of patients experiencing Radiotherapy Oncology Group (RTOG) toxicity grades 1 and 2 in those patients in the elemental group vs. those consuming a standard diet group, but did not report a significance value.[36] However, a significant decrease in the number of patients whose treatment was interrupted due to toxicity in the elemental group vs. the standard diet group was reported. In three further studies,[35, 37, 38] no significant

Table 1 | Summary of interventions and effects: RCT studies only

Reference	Study design: Intention RCT/CT	Quality Score	Intervention	Effect of intervention on GI toxicity end-points
Elemental formulae				
35	RCT Open-label: Preventative	7	Low-fibre diet vs. low-fibre diet plus elemental formula (900kcals/d)	No difference compared to low-fibre diet
36	RCT Open-label: Preventative	4	Standard diet vs. natural diet plus elemental formula (33% TE)	Improved outcomes compared to standard diet
37	RCT Open-label: Preventative	10	Normal diet vs. normal diet with elemental formula (33% TE)	No difference compared to normal diet
38	RCT Open-label: Preventative	7	Low-fibre diet vs. low-fibre diet plus elemental formula (900 kcals/d)	No difference compared to low-fibre diet
Low- or modified-fat diets				
21	RCT Open-label: Preventative	8	Normal diet vs. low-lactose low-fat diet (40 g/d)	Improved outcomes compared to normal diet
25	RCT Double-blind placebo: Therapeutic	12	Low-fat diet (40 g/d) plus placebo vs. low-fat diet (40 g/d) plus cholestyramine	Improved outcomes compared to placebo
41	RCT Open-label: Preventative	3	Low-fat diet (20 g/d) vs. low-fat diet (20 g/d) plus MCT supplement (50% TE)	Improved outcomes compared to normal diet
42	RCT Open-label: Preventative	13	Normal diet (LCT 40% TE) vs. Low-fat (LCT 20%) vs. Low-fat (LCT 20%) plus MCT (20%)	No difference compared to normal or MCT-supplemented diet
Low- or high-fibre diets				
43	RCT Open-label: Crossover: Therapeutic	9	Standard medication (codeine phosphate) vs. fibre supplement (psyllium)	Worse outcome for fibre supplement compared to medication
45	RCT Open-label: Preventative	8	Low-fibre and fat (LFF) diet vs. LFF diet plus fibre supplement (psyllium)	Improved outcomes compared to low-(dietary) fibre low-fat diet
Low-lactose diets				
48	RCT Open-label: Preventative	6	Normal lactose vs. low-lactose vs. normal lactose plus enzyme	No difference between groups
Probiotics and Synbiotics				
49	RCT Open-label: Preventative	5	Low-fibre, fat and lactose(LFFL) diet vs. LFFL diet plus synbiotic	Improved outcomes compared to LFFL diet alone
50	RCT Double-blind placebo: Therapeutic	14	Placebo vs. probiotic	No difference compared to placebo
51	RCT Double-blind placebo: Preventative	5	Placebo vs. probiotic	Improved outcomes compared to placebo
52	RCT Double-blind placebo: Preventative	12	Placebo vs. probiotic	Improved outcomes compared to placebo
53	RCT Double-blind placebo: Preventative	12	Placebo vs. probiotic	Improved outcomes compared to placebo

differences between elemental and non-intervention groups were reported in mean stool frequency,[35] time to onset of diarrhoea,[35] change in Inflammatory Bowel Disease Questionnaire-bowel score (IBDQ-B),[37] change in faecal calprotectin[37] or change in markers of nutritional status.[38] Compliance with elemental prescription was a concern. In one study,[35] 41% of patients were unable to tolerate the elemental formula for the prescribed period and in another study, mean dose of formula taken was just 21% of daily energy requirement compared to the prescribed 33%.[37]

Two further nonrandomised studies have been reported. A phase II investigation of 17 patients with gynaecological cancer receiving a 4/5 week course of treatment,[39] which additionally asked patients to reduce fibre, lactose and fat, reported a significant reduction in the proportion of compliant patients experiencing RTOG grade 2/3 diarrhoea ($P < 0.001$) together with reduced

need for antidiarrhoeal medication.[39] Compliance was reportedly high in the elemental group with 76.5% of patients taking the prescribed formula for >80% of the time. The second nonrandomised trial commenced as an RCT in patients receiving presurgical, short course radiotherapy for invasive bladder cancer.[40] The duration of the intervention period was just 5 days with elemental formula providing 100% of energy intake.[40] Randomisation to the conventional feeding group (normal hospital diet or parenteral nutrition) was halted after a benefit was identified in just four patients receiving elemental feeding.[40] The authors reported a significant reduction in the incidence of severe post-operative diarrhoea in elementally fed patients when compared with a retrospective group receiving conventional feeding ($P < 0.001$).

Summary. Evidence for the efficacy of elemental formula from RCTs is weak. Whilst the sole study[36] that did report improved outcomes was by far the largest, it is published in abstract only and was judged to have a low quality score (Table 1). Three higher quality studies failed to provide evidence of efficacy, although these suffered from poor compliance, and thus it is unclear whether the intervention itself was ineffective or the lack of end-points in noncompliant patients resulted in underpowering.[35, 37, 38] One non-RCT in which diet was completely replaced with elemental formula provided evidence of efficacy in presurgical patients in a short-term setting albeit using retrospective controls.[40] Whether 100% replacement of normal diet with elemental formula could be achieved in patients during long course radiotherapy is debatable.

Low- or modified-fat diets

Rationale. In the UK, dietary reference values (DRVs) for fat intake are that fat should comprise approximately one-third of total caloric requirements, approximately 95 g fat/day (males) and 70 g fat/day (women).[59] Dietary fats comprise long-chain triacylglycerols (LCTs) with three fatty acids, mostly 12–18 carbon units in length. In contrast, medium-chain triacylglycerols (MCTs) comprise 8–14 carbon fatty acids that are absorbed directly into portal blood. They occur in only a few foods (e.g. coconut), but may be prescribed in supplement form under medical or dietetic supervision. The rationale for the use of low- or modified-fat (MCT-predominant) diets during radiotherapy is four-fold. Damage to the gastrointestinal brush border[60] may reduce its ability to absorb LCTs, high-fat (LCT-based) diets may be pro-inflammatory,[61] reduced production of bile acids may occur[25, 62] and MCTs do not stimulate exocrine pancreatic secretions (specifically amylase and lipase)[63] sparing gastrointestinal mucosa from the proteolytic effects of these enzymes.

Evidence. Four RCTs recruiting 316 patients[21, 25, 41, 42] have examined the efficacy of low- or modified-fat diets in preventing radiation toxicity. Dietary interventions were used in all four studies with the low LCT fat groups consuming 20 g/day[41] or 40 g/day.[21, 25, 42] Intervention strategies differed, two studies[41, 42] used MCT-based supplements to compensate for reduced total energy intake, lactose was additionally restricted in one study[21] and in another,[25] all patients were instructed to follow a low-fat diet, but were randomised at 2 weeks to receive the bile acid binder cholestyramine (4 g twice daily) or placebo. Two studies[21, 25] reported benefits associated with a low-fat diet. In one, significant differences between patients consuming a low-fat, low-lactose diet vs. patients on a regular hospital diet were reported including a halving of the incidence of new onset diarrhoea, a 50% reduction in the mean number of antidiarrhoeal tablets used ($P < 0.01$) and a significant reduction in the number of loose, watery stools per week ($P < 0.01$).[21] In the other study, diarrhoea control was significantly better ($P < 0.05$) in the cholestyramine arm, although >50% patients in this group reported side effects including nausea and abdominal cramps.[25]

In the remaining two studies, one reported reduced bowel frequency in the low-fat MCT-supplemented group vs. the low-fat group; however, these results were not significant and the difference in frequency, modest (mean 1.6 ± 0.9 vs. 2.0 ± 1.0 stools per day).[41] The other study used a 3-arm design to compare a normal fat diet vs. low-fat vs. low-fat and MCT supplement (50:50 ratio of LCT: MCT) and reported no significant difference in the change in IBDQ-B scores or change in secondary nutritional end-points between groups. Poor compliance in the normal fat group[42] resulted in the majority of patients consuming a diet with low LCT content. The authors commented that the fall in IBDQ-B score for the cohort ($n = 107$) compared favourably with a mean pooled fall of 9 points from previous studies in similar cohorts ($n = 409$), suggesting a positive impact of dietary intervention (irrespective of study arm) and/or a benefit of reduced fat intake across all groups.[2, 23, 30, 37]

Summary. Evidence for the efficacy of low LCT fat interventions is limited. Whilst two high-quality RCT provided evidence of efficacy, neither manipulated fat as the sole intervention making it difficult to determine which

intervention was responsible for efficacy.[21, 25] Although a third RCT[41] reported a modest benefit of low fat, it is published in abstract only and achieved a low quality score (Table 1). The final adequately powered high-quality study found no significant difference in outcomes between groups, although inadequate differential in fat intake between groups precluded robust conclusions.[42]

Dietary Fibre

Rationale. The definition of fibre has been debated for years and measurement techniques vary. In 2008, a Codex (Codex Alimentarius Commission) Committee on Nutrition and Foods for Special Dietary Uses agreed on a definition of dietary fibre as 'carbohydrate polymers with ten or more monomeric units which are not hydrolysed by endogenous enzymes in the small intestine of human beings'.[64] This definition encompasses naturally occurring, edible, plant-based polymers found in fruits, vegetables, seeds, nuts and cereals (i.e. items promoted as components of a healthy diet) and also extracted or synthetic carbohydrate polymers with proven physiological effects. Naturally occurring dietary fibre comprises both soluble and insoluble fractions with distinct properties. Both fractions occur naturally in most foods, but one or the other normally predominates in extracted or synthetic supplements. Insoluble fibre is less completely fermentable than soluble fibre and provides stool bulk and promotes motility. Soluble fibre (e.g. psyllium) provides a fermentable substrate for the gastrointestinal microbiota, producing short-chain fatty acids (SCFA), of which butyrate has received much attention due to its trophic, immune-modulatory and anti-inflammatory actions.[65, 66] A recent meta-analysis suggested that fibre has a unique moderating effect with the ability to both reduce bowel frequency when undesirably high and yet increase it when too low.[67]

Evidence. Four studies[43–46] recruiting 275 patients and comprising two RCT[43, 45] and two case series[44, 46] have explored the benefit of manipulating dietary and/or supplemental fibre during pelvic irradiation. Three studies[44–46] explored the preventative role of fibre in reducing gastrointestinal toxicity, whilst a fourth study[43] explored the therapeutic efficacy of the psyllium vs. codeine phosphate for the control of radiation-induced diarrhoea.[43] One RCT reported reduced incidence ($P = 0.049$) and severity ($P = 0.030$) of diarrhoea (using a nonvalidated scale) in patients following a low-fibre, low-stimulant (caffeine and alcohol), low-fat diet plus psyllium supplement vs. those following the diet alone.[45] This study also reported reduced need for antidiarrhoeal medication in the diet plus psyllium group, although the difference between groups was not significant. The other RCT instructed all patients to follow a low-fibre diet and used a crossover design to compare the efficacy of psyllium with codeine phosphate on presentation of treatment-induced diarrhoea.[43] This study was terminated early after recruitment of ten patients due to lack of efficacy of psyllium, with all patients crossed-over to codeine phosphate.

Two further case series[44, 46] have reported favourable effects of reduced[44] or increased fibre consumption.[46] A large retrospective study imposed dietary restrictions (low residue, restricted caffeine, alcohol and spicy foods) in 156 prostate cancer patients and reported improved genitourinary and gastrointestinal symptoms in compliant vs. noncompliant patients. Noncompliant patients all experienced side effects and grade 1 toxicity (41% of patients) was easily managed by reinforcement of dietary advice. In the smaller prospective study[46] ($n = 22$), prostate cancer patients were given individual advice to increase dietary fibre and fluid with the aim of stabilising rectal dimensions to prevent prostate deformation during treatment. Improved IBDQ-B scores were reported in those who met their fibre prescription vs. those who did not.

Summary. Evidence for the efficacy of fibre is weak. No high-quality RCTs have been conducted (Table 1). One RCT that reported a benefit used nonvalidated outcomes and manipulated both dietary fat and fibre, whilst additionally giving a fibre supplement.[45] In the other RCT, worse outcomes with a fibre supplement vs. a pharmacological preparation were reported.[43] Evidence from case series is inconclusive. Whilst the prospective series reported positive outcomes with higher fibre intake, the study was small and not powered for toxicity endpoints.[46]

Lactose restriction

Rationale. Lactose is a disaccharide of glucose and galactose found in milk and milk products. Typical quantities are 13.5 g/half pint (284 mL) of full cream or skimmed milk with similar amounts in other dairy products such as yoghurt and ice cream. Lactose must be cleaved to its monomeric units by the enzyme lactase present in the brush border, prior to absorption. Unabsorbed lactose contributes to an osmotic load in the colon causing watery diarrhoea. In many races, a genetically

programmed fall in lactase occurs after weaning resulting in intolerance to lactose. In white Caucasian populations, endogenous lactase does not diminish with adulthood, although genetic lactase deficiency can occur in 5–19% of adults. Interestingly, it is not unusual for adults to mistakenly attribute abdominal symptoms to lactose intolerance; however, an important study found that most adults can actually consume small amounts of lactose without any problem and that only large doses actually elicit symptoms.[68] Lactase deficiency may arise secondary to radiation-induced damage of the intestinal mucosa and depletion of brush border enzymes. Although the incidence of new-onset lactose intolerance during radiotherapy has not been definitively quantified, one small study[23] in a cohort of 26 patients has suggested that it may be about 15%.

Evidence. Three studies recruiting 118 patients have examined the incidence of lactose malabsorption[22, 47] and the efficacy of a lactose restricted or modified diet during treatment.[48] Two prospective case series[22, 47] in white Caucasian cohorts have demonstrated new-onset lactose intolerance during pelvic radiotherapy. In the first of these studies, 12/24 (50%) patients exhibited significantly reduced lactose absorption as assessed by ^{14}C lactose breath test[22] and a significant correlation was reported between the breath test results at 5 weeks and increased stool frequency, suggesting that patients with the most marked lactose malabsorption also had the most severe diarrhoea. A later study by the same group investigated the impact of volume of small bowel irradiated on lactose malabsorption[47] and found a clear separation in absorption rates in patients with large bowel volumes within the radiotherapy field compared with those with smaller volumes, but there was no correlation between the change in breath test and stool frequency in either group.

Only one RCT has examined the efficacy of lactose-restricted diets during pelvic radiotherapy.[48] In a 3-arm study in which 64 mixed pelvic site patients were randomised to follow diets [supplemented with 480 mL milk] vs. [lactose restriction, amounts not reported] vs. [supplemented with 480 cc milk + lactase enzyme], no benefit was found in any arm on multivariate analysis in reduced stool frequency or number of diarrhoea tablets used. The authors suggested that delayed gastric emptying following 5 weeks of radiotherapy may have confounded breath test results in the earlier studies[22, 47] and/or that sites of maximal lactose absorption (mid-jejunum and upper ileum) escaped irradiation and/or that other factors (e.g. bile acid malabsorption) overwhelmed any benefit of the lactose restriction.

Summary. Whilst it is acknowledged that true lactose malabsorption is less prevalent than commonly supposed,[68] limited evidence suggests that patients can become lactose-intolerant during pelvic radiotherapy, but there is no evidence that restricting its consumption (or providing it in prehydrolysed form) is helpful. The sole RCT found no difference between groups in relevant gastrointestinal end-points.[48] Whilst this study used an elegant design, the published paper lacked data on study powering (Table S2), and given the 17% drop out, the possibility of a type II error cannot be ruled out.

Probiotics, Prebiotics, Synbiotics

Rationale. Probiotics are live microorganisms (bacteria) that, when administered in adequate amounts, confer a health benefit on the host.[69] They include (but are not limited to) lactobacilli and bifidobacteria species and remain viable after passage through the human stomach and small intestine. 'A prebiotic is a selectively fermented ingredient that allows specific changes, in the composition and/or activity in the gastrointestinal microbiota that confers benefits on host wellbeing and health'.[70] Prebiotics include inulin, lactulose and the short-chain carbohydrates fructo-oligosaccharides ('oligofructose') and galacto-oligosaccharides. Synbiotics are combinations of probiotics and prebiotics.

There are a variety of mechanisms through which probiotics exert their effects. These include modification in the incumbent microbiota population to favour non-pathogenic species, by reducing luminal pH, competitive inhibition of pathogenic strains and secretion of anti-pathogenic compounds including bacteriocidins and defensins. Probiotics also exert additional beneficial immunomodulatory effects on local mucosal and systemic immune systems.[71] Prebiotics provide a substrate for the preferential growth of nonpathogenic species resulting in the enhanced production of SCFA, which promote optimal colonic fluid balance, stimulate water and sodium absorption and preserve mucosal barrier function.[65] Synbiotics offer a potentially synergistic option, but differ in efficacy depending on the specific combination.

Evidence. Five RCT recruiting 901 patients[49–53] have examined the efficacy of probiotic or synbiotic preparations. Outcomes for the largest study[51] are reported in

three separate publications,[51, 54, 55] but here, quality is assessed with reference to one publication.[51] Four of the studies are preventative in aim[49, 51–53] and one, therapeutic.[50] In the earliest open-label study,[49] twenty-four patients were randomised to receive either a synbiotic comprising 2×10^9 radiation-resistant *Lactobacillus acidophilus* plus 8 g/day lactulose in addition to a low-fibre, low-lactose, low-fat diet or diet alone. The incidence of diarrhoea was significantly reduced in the synbiotic plus diet group ($P < 0.01$) vs. the diet alone group. The authors postulated that the synbiotic decreased faecal pH and favourably altered faecal microbiota, features that had been demonstrated in earlier work but remain unpublished. In a later double-blind, therapeutic study,[50] 206 patients were randomised to receive either a probiotic containing 1.5 g of *L. rhamnosus* (1.5×10^9 CFU) or placebo to manage treatment-induced mild-to-moderate diarrhoea. No significant difference was found between groups in the time to use of, or frequency of use of 'rescue' diarrhoea medication.

The largest study to date used a double-blind, placebo-controlled design to test the efficacy of the probiotic VSL#3, comprising 8 different bacterial strains (450×10^9 CFU) to reduce treatment-induced gastrointestinal toxicity assessed using the World Health Organisation (WHO) 5-point grading scale.[51] Earlier reports of the same cohort were published ($n = 190$ patients)[54, 55] in which it was stated that patients were additionally instructed to follow a hypercaloric diet (due to 'radiotherapy-induced metabolic stress'), which entailed restricting fat and fructose, but maintaining a normal fibre intake.[54] However, it is not clear whether these additional dietary instructions applied to all those recruited to this study. A significantly reduced number of patients in the probiotic group vs. placebo experienced 'radiation-induced enteritis and colitis' (31.6% vs. 51.8% respectively, $P < 0.001$) although this condition remained undefined by the authors and a significantly higher proportion of patients in the placebo group experienced grade 3 or 4 toxicity ($P < 0.001$). The daily number of bowel movements for patients with radiation-induced diarrhoea was reduced ($P < 0.005$) in the probiotic group vs. placebo (5.1 ± 3 vs. 14.7 ± 6) together with significantly increased ($P < 0.001$) mean time to use of rescue diarrhoea medication.

In a later double-blind study, $n = 118$ patients were randomly assigned to receive a probiotic drink (10^8 CFU/g of *L. casei*) or placebo.[52] Whilst patients in the probiotic group had a significantly improved stool consistency ($P = 0.04$) including greater median time before experiencing Bristol stool type ≥ 6 (14 days vs. 10), there was no significant difference between groups in the need for antidiarrhoeal medication or incidence of Common Toxicity Criteria (CTC) grade-2 toxicity. The most recent study also used a double-blind design and randomised 63 patients to receive a probiotic preparation (10^9 *L. acidophilus* and 10^9 *Bifidobacterium bifidum*) or placebo starting 7 days prior to radiotherapy and continuing during treatment.[53] Significantly fewer patients in the probiotic group experienced CTC grade ≥ 2 diarrhoea vs. the placebo group ($P = 0.002$). Use of antidiarrhoeal medication was also significantly reduced ($P = 0.03$) together with improved stool consistency ($P < 0.001$) in the probiotic group vs. placebo group.

Summary. There is limited evidence for the efficacy of probiotics in reducing diarrhoea acutely. However, the methodological quality of studies varied widely with the largest study[51] scoring a low quality score (Table 1). Of the two high-quality studies[52, 53] reporting a benefit, one achieved only 55% of planned recruitment and failed to find a significant difference between groups in the primary outcome, although reported improvements in secondary outcomes, and the other only partly addressed the issue of study powering (Table S2) and did not state a specific end-point.[53]

DISCUSSION

With the burden of cancer doubling globally between 1975 and 2000 and survival in the UK continuing to rise by 3% per annum,[72] it is appropriate to explore strategies to prevent or reduce gastrointestinal toxicity resulting from therapeutic radiotherapy for pelvic cancers. Nutritional intervention is often a low-cost option with sound scientific rationale. This review has identified twenty-two original studies, recruiting 2446 patients to five major dietary interventions: elemental, low-/modified-fat, fibre, lactose restriction and probiotic or synbiotic interventions. The studies vary widely in design with 16 being RCT, of which 13 were preventative studies and three therapeutic. Only five studies (four probiotic interventions and one therapeutic study) used a double-blind design.[25, 50–53] The difficulty of providing sham diets is acknowledged and thus all dietary interventions were open-label. However, only 50% of studies used a sole dietary intervention, whilst the remaining studies either failed to define this accurately or used multiple interventions making it impossible to determine the active component.

Similarly, study quality was highly variable. We used a bespoke quality assessment tool for this review and

acknowledge that quality scoring has its limitations; however, of the 16 RCT, only six studies scored ≥ 10 points of the maximum 17 points available. Excluding 'adequate concealment', which was the most frequent quality criteria not met (mostly because it was not stated), many studies failed to provide details of study powering or nominate a primary end-point nor provided an analysis of compliance, the latter being essential to nutritional intervention RCTs. Given the diverse range of outcomes and comparators, we have not attempted meta-analysis nor undertaken any formal statistical analysis of bias (e.g. publication bias).

Of all nutritional interventions in this review, probiotic supplementation appears to offer the most promise as a prophylactic for positively influencing toxicity outcomes. From a practical perspective, probiotic supplementation may also represent a more easily achievable approach than dietary manipulation. However, our knowledge about the precise mix of dynamic and diverse microbiota that inhabits the human gastrointestinal tract is still limited and is highly individual. Attempting to manipulate such an ill-defined ecosystem should be approached with caution especially as our methods of analysing the effects of such supplementation on the incumbent microbiota are still relatively crude outside the research setting. The probiotic interventions discussed above used differing doses and combinations of strains each of which should be appropriately tested prior to introduction to clinical practice. Furthermore, only three of the five probiotic studies provided details of concomitant chemotherapy agents, which are used increasingly in combination with radiotherapy. Immunosuppressed patients may respond differently and represent a higher risk group so probiotic intervention in these patients must be preceded by preliminary safety trials with appropriate data monitoring, clinical governance and accurate and visible adverse event reporting.[73]

In summary, there is insufficient high-grade evidence to recommend any of the nutritional interventions in this review be implemented in clinical practice. Restrictive low-lactose, low-fat and low-fibre diets should not be recommended during radical pelvic radiotherapy unless a clear clinical rationale is provided or unless their efficacy is explored within the context of an appropriate RCT. If so, they should only be implemented with appropriate dietetic monitoring. Total replacement of diet with elemental formula can probably only be achieved after placement of a nasogastric or gastrostomy tube and the evidence does not support its use except in exceptional clinical settings or within the context of clinical trials. High-dose probiotic preparations should not be implemented until full safety testing of each individual preparation is completed.

AUTHORSHIP

Guarantor of the article: None.

Author contributions: HJNA and LJW designed the study. CS reviewed the text and provided expert dietetic comment. KW contributed to the presentation and synthesis of results. LJW conducted the literature searches, extracted information, designed the quality analysis tool and wrote the initial draft of the manuscript. All authors approved the final version of the manuscript.

ACKNOWLEDGEMENTS

Declaration of personal interests: The significant contribution of Dr C. McGough's extensive research (embodied within her PhD) provided the backdrop for this update.

Declaration of funding interests: None.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1. Randomised controlled trials, controlled trials and case series of acute nutritional interventions in adult patients receiving pelvic radiotherapy.

Table S2. Quality analysis.

REFERENCES

1. Hoskin P (Ed.) *]Radiotherapy in Practice. External Beam Therapy*. Oxford, UK: Oxford University Press, 2006.
2. Khalid U, McGough C, Hackett C, *et al.* A modified inflammatory bowel disease questionnaire and the Vaizey incontinence questionnaire are more sensitive measures of acute gastrointestinal toxicity during pelvic radiotherapy than RTOG grading. *Int J Radiat Oncol Biol Phys* 2006; **64**: 1432–41.
3. Gami B, Harrington K, Blake P, *et al.* How patients manage gastrointestinal symptoms after pelvic radiotherapy. *Aliment Pharmacol Ther* 2003; **18**: 987–94.
4. Olopade F, Norman A, Blake P, *et al.* A modified inflammatory bowel disease questionnaire and the Vaizey incontinence questionnaire are simple

ways to identify patients with significant gastrointestinal symptoms after pelvic radiotherapy. *Br J Cancer* 2005; **9**: 1663–70.
5. Bergmark K, Avall-Lundquist E, Dickman P. Patient rating of distressful symptoms after treatment for early cervical cancer. *Acta Obstet Gynecol Scand* 2002; **81**: 443–50.
6. al Abany M, Helgason A, Cronqvist A. Long-term symptoms after external beam radiation therapy for prostate cancer with three or four fields. *Acta Oncol* 2002; **41**: 532–42.
7. Henningsohn L, Wijkstrom H, Dickman D. Distressful symptoms after radical radiotherapy for urinary bladder cancer. *Radiother Oncol* 2002; **62**: 215–25.
8. Fokdal L, Hoyer M, Meldgaard P, von der Masse H. Long-term bladder, colorectal, and sexual functions after radical radiotherapy for urinary bladder cancer. *Radiother Oncol* 2004; **72**: 139–45.
9. Crook J, Esche B, Futter N. Effect of pelvic radiotherapy for prostate cancer on bowel, bladder, and sexual function: the patient's perspective. *Urology* 1996; **47**: 387–94.
10. Denham JD, Hauer-Jensen M. The radiotherapeutic injury – a complex 'wound'. *Radiother Oncol* 2002; **63**: 129–45.
11. Hovdenak N, Fajardo LF, Hauer-Jensen M. Acute radiation proctitis: a sequential clinicopathologic study during pelvic radiotherapy. *Int J Radiat Oncol Biol Phys* 2000; **48**: 1111–7.
12. Larsen A, Bjorge B, Klementsen B, *et al.* Time patterns of changes in biomarkers, symptoms and histopathology during pelvic radiotherapy. *Acta Oncol* 2007; **46**: 639–50.
13. Andreyev HJN, Wotherspoon A, Denham J, Hauer-Jensen M. Comment: defining pelvic-radiation disease for the survivorship era. *Lancet Oncol* 2010; **11**: 310–2.
14. Sullivan MF. Dependence of radiation diarrhoea on the presence of bile in the intestine. *Nature* 1962; **195**: 1217–8.
15. Mulholland M, Levitt S, Song C, Potish R, Delaney J. The role of luminal contents in radiation enteritis. *Cancer* 1984; **54**: 2396–402.
16. Sokol A, Lipson L, Morgenstern L, Hiatt N. Protection against lethal irradiation injury by pancreatic enzyme exclusion. *Surg Forum* 1967; **18**: 387–9.
17. Morgenstern L, Patin C, Krohn H. Prolongation of survival in lethally irradiated dogs. *Arch Surg* 1970; **101**: 586–9.
18. Hauer-Jensen M, Sauer T, Berstad T. Influence of pancreatic secretion on late radiation enteropathy in the rat. *Acta Radiol Oncol* 1985; **24**: 555–60.
19. Wang J, Zheng H, Sung C. The synthetic somatostatin analogue, octreotide, ameliorates acute and delayed intestinal radiation injury. *Int J Radiat Oncol Biol Phys* 1999; **45**: 1289–96.
20. Wang J, Zheng H, Hauer-Jensen M. Influence of short-term octreotide administration on chronic tissue injury, transforming growth factor b (TGF-b) overexpression, and collagen accumulation in irradiated rat intestine. *J Pharmacol Exp Ther* 2001; **297**: 35–42.
21. Bye A, Kaasa S, Ose T, Sundfor K, Trope C. The influence of low fat, low lactose diet on diarrhoea during pelvic radiotherapy. *Clin Nutr* 1992; **11**: 147–53.
22. Stryker J, Mortel R, Hepner G. The effect of pelvic irradiation on lactose absorption. *Int J Radiat Oncol Biol Phys* 1978; **4**: 859–63.
23. Wedlake L, Thomas K, McGough C, Andreyev HJN. Small bowel bacterial overgrowth and lactose intolerance during radical pelvic radiotherapy: an observational study. *Eur J Cancer* 2008; **44**: 2212–7.
24. Andersson H, Bosaeus I, Nystrom C. Bile salt malabsorption in the radiation syndrome. *Acta Radiol Oncol Radiat Phys Biol* 1978; **17**: 312–8.
25. Chary S, Thompson D. A clinical trial evaluating cholestyramine to prevent diarrhea in patients maintained on low-fat diets during pelvic radiation therapy. *Int J Radiat Oncol Biol Phys* 1984; **10**: 1885–90.
26. Yeoh EK, Horowitz M, Russo A, Muecke T, Robb T, Maddox A. Effect of pelvic irradiation on gastrointestinal function. *Am J Med* 1993; **95**: 397–406.
27. Husebye E, Skar V, Hoverstad T, Iversen T, Melby K. Abdominal intestinal motor patterns explain enteric colonization with gram-negative bacilli in late radiation enteropathy. *Gastroenterology* 1995; **109**: 1078–89.
28. Wang CJ, Leung SW, Chen HC, *et al.* The correlation of acute toxicity and late rectal injury in radiotherapy for cervical carcinoma: evidence suggestive of consequential late effect (CQLE). *Int J Radiat Oncol Biol Phys* 1998; **40**: 85–91.
29. Heemsbergen WD, Peeters STH, Koper PCM, Hoogeman MS, Lebesque JV. Acute and late gastrointestinal toxicity after radiotherapy in prostate cancer patients: consequential late damage. *Int J Radiat Oncol Biol Phys* 2006; **66**: 3–10.
30. Wedlake LJ, Thomas K, Lalji A, *et al.* Predicting late effects of pelvic radiotherapy: is there a better approach? *Int J Radiat Oncol Biol Phys* 2010; **78**: 1163–70.
31. Jadad AR, Moore RA, Carroll D, *et al.* Assessing the quality of reports of randomised clinical trials: is blinding necessary? *Control Clin Trials* 1996; **17**: 1–12.
32. Juni P, Altman DG, Egger M. Assessing the quality of controlled clinical trials. *BMJ* 2001; **323**: 42–6.
33. McGough C, Baldwin C, Frost G, Andreyev HJN. Role of nutritional intervention in patients treated with radiotherapy for pelvic malignancy. *Br J Cancer* 2004; **90**: 2278–87.
34. Fuccio L, Guido A, Eusebi LH, *et al.* Effects of probiotics for the prevention and treatment of radiation-induced diarrhoea. *J Clin Gastroenterol* 2009; **43**: 506–13.
35. Brown M, Buchanan R, Karran S. Clinical observations on the effects of elemental diet supplementation during irradiation. *Clin Radiol* 1980; **31**: 19–20.
36. Capirci C, Polico C, Amichetti M, *et al.* Diet prevention of radiation acute enteric toxicity: multicentric randomised study. *Radiother Oncol* 2000; **56**(Suppl. 1): S44.
37. McGough C, Wedlake L, Baldwin C, *et al.* Clinical trial: normal diet vs. partial replacement with oral E028 formula for the prevention of gastrointestinal toxicity in cancer patients undergoing pelvic radiotherapy. *Aliment Pharmacol Ther* 2008; **27**: 1132–9.
38. Foster K, Brown M, Alberti K, *et al.* The metabolic effects of abdominal irradiation in man with and without dietary therapy with an elemental diet. *Clin Radiol* 1980; **31**: 13–7.
39. Craighead P, Young S. Phase II study assessing the feasibility of using elemental supplements to reduce acute enteritis in patients receiving radical pelvic radiotherapy. *Am J Clin Oncol* 1998; **21**: 573–8.
40. McArdle A, Reid E, Laplante M, Freeman C. Prophylaxis against radiation injury. The use of elemental diet prior to and during radiotherapy for invasive bladder cancer and in early postoperative feeding following radical cystectomy and ileal conduit. *Arch Surg* 1986; **121**: 879–85.
41. Karlson S, Kahn JM, Portman W, Simonsen E, Onk Klin G. A randomised trial with low fat diets to improve food intake and tolerance in women receiving abdominal radiotherapy for cancer. *Clin Nutr* 1989; **8**(Special Suppl.): 39
42. Wedlake L, McGough C, Shaw C, *et al.* Clinical Trial: efficacy of a low or

modified fat diet for the prevention of gastrointestinal toxicity in patients receiving radiotherapy for pelvic malignancies. *J Hum Nutr Diet* 2012; **25**: 247–59.
43. Lodge N, Evans ML, Wilkins M, Blake P, Fryatt I. A randomised cross-over study of the efficacy of codeine phosphate versus Ispaghulahusk in patients with gynaecological cancer experiencing diarrhoea during pelvic radiotherapy. *Eur J Cancer Care* 1995; **4**: 8–10.
44. Liu L, Glicksman A, Coachman N, Kuten A. Low acute gastrointestinal and genitourinary toxicities in whole pelvic irradiation of prostate cancer. *Int J Radiat Oncol Biol Phys* 1997; **38**: 65–71.
45. Murphy J, Stacey D, Crook J, Thompson B, Panetta D. Testing control of radiation-induced diarrhoea with psyllium bulking agent: a pilot study. *Can Oncol Nurs J* 2000; **10**: 96–100.
46. McNair HA, Wedlake LJ, McVey G, Thomas K, Andreyev J, Dearnaley DP. Can diet combined with treatment scheduling achieve consistency of rectal filling in patients receiving radiotherapy to the prostate? *Radiother Oncol* 2011; **101**: 471–8.
47. Weiss RG, Stryker JA. 14C-Lactose breath tests during pelvic radiotherapy: the effect of the amount of small bowel irradiated. *Radiology* 1982; **142**: 507–10.
48. Stryker JA, Bartholomew M. Failure of lactose-restricted diets to prevent radiation-induced diarrhoea in patients undergoing whole pelvis irradiation. *Int J Radiat Oncol Biol Phys* 1986; **12**: 789–92.
49. Salminen E, Elomaa I, Minkkinen J, Vapaatalo H, Salminen S. Preservation of intestinal integrity during radiotherapy using live lactobacillus acidophilis cultures. *Clin Radiol* 1988; **39**: 435–7.
50. Urbancsek H, Kazar T, Mezes I, Neumann K. Results of a double-blind, randomised study to evaluate the efficacy and safety of Antibiophilus in patients with radiation-induced diarrhoea. *Eur J Gastroenterol Hepatol* 2001; **13**: 391–6.
51. Delia P, Sansotta G, Donato V, *et al.* Use of probiotics for prevention of radiation-induced diarrhea. *World J Gastroenterol* 2007; **13**: 912–5.
52. Giralt J, Regadera JP, Verges R, *et al.* Effects of probiotic lactobacillus casei DN-114 001 in the prevention of radiation-induced diarrhea: results from multicentre, randomised, placebo-controlled nutritional trial. *Int J Radiat Oncol Biol Phys* 2008; **71**: 1213–9.
53. Chitapanarux I, Chitapanarux T, Traisathit P, Kudumpee S, Tharavichitkul E, Lorvidhaya V. Randomised controlled trial of live lactobacillus acidophilus plus bifidobacterium in prophylaxis of diarrhea during radiotherapy in cervical cancer patients. *Radiat Oncol* 2010; **5**: 31.
54. Delia P, Sansotta G, Donato V, *et al.* Prophylaxis of diarrhoea in patients submitted to radiotherapeutic treatment on pelvic district: personal experience. *Dig Liver Dis* 2002; **34**(Suppl. 2): S84–6.
55. Delia P, Sansotta G, Donato V, *et al.* Prevention of radiation-induced diarrhoea with the use of VSL#3, a new high-potency probiotic preparation. *Am J Gastro* 2002; **97**: 2150–2.
56. Kaushik N, Pietraszewski M, Holst J, O'Keefe S. Enteral feeding without pancreatic stimulation. *Pancreas* 2005; **31**: 353–9.
57. Vu M, Van der Veek P, Frolich M, *et al.* Does jejunal feeding activate exocrine pancreatic secretion? *Eur J Clin Invest* 1999; **29**: 1053–9.
58. O'Keefe S, Lee R, Anderson F, *et al.* Physiological effects of enteral and parenteral feeding on pancreatobiliary secretion in humans. *Am J Physiol Gastrointest Liver Physiol* 2002; **284**: G27–36.
59. Department of Health. *]Report on Health and Social Subjects no. 41. Dietary Reference Values for Food Energy and Nutrients for the United Kingdom. Report of the Panel on Dietary Reference Values of the Committee on Medical Aspects of Food Policy*. London: HMSO, 1991.
60. Hauer-Jensen M, Wang J. Denham J Bowel injury: current and evolving management strategies. *Semin Radiat Oncol* 2003; **13**: 357–71.
61. Middleton SJ, Rucker JT, Kirby GA, Riordan AM, Hunter JO. Long-chain tryglycerides reduce the efficacy of enteral feeds in patients with active Crohn's disease. *Clin Nutr* 1995; **14**: 229–36.
62. Boseaus I, Andersson H, Nystro C. Effect of a low-fat diet on bile salt excretion and diarrhoea in the gastrointestinal radiation syndrome. *Acta Radiol Oncol* 1979; **18**: 460–4.
63. Symersky T, Vu M, Frolich M, Biemond I, Masclee A. The effect of equicaloric medium-chain and long-chain triglycerides on pancreas enzyme secretion. *Clin Physiol Funct Imaging* 2002; **22**: 307–11.
64. Cummings JH, Mann JI, Hishida C, Vorster HH. Dietary fibre: an agreed definition. *Lancet* 2009; **373**: 365–6.
65. Cook SI, Selin JH. Review article: short chain fatty acids in health and disease. *Aliment Pharmacol Ther* 1998; **12**: 449–507.
66. Hamer HM, Jonkers D, Venema K, Vanhoutvin S, Troost FJ. Review article: the role of butyrate on colonic function. *Aliment Pharmacol Ther* 2008; **27**: 104–19.
67. Elia M, Engfer MB, Green CJ, Silk DBA. Systematic review and meta-analysis: the clinical and physiological effects of fibre-containing enteral formulae. *Aliment Pharmacol Ther* 2007; **27**: 120–45.
68. Suarez F, Savaiano D, Levitt MD. A comparison of symptoms after the consumption of milk or lactose-hydrolysed milk by people with self-reported severe lactose intolerance. *N Engl J Med* 1995; **333**: 1–4.
69. Food and Agriculture Organisation of the United Nations and World Health Organisation Working Group. *] Guidelines for the Evaluation of Probiotics in Food*. Geneva, Switzerland: FAO/WHO, 2002.
70. Gibson GR, Probert HM, Van Loo J, Rastall RA, Roberfroid MB. Dietary modulation of the human colonic microbiota: updating the concept of prebiotics. *Nutr Res Rev* 2004; **17**: 59–275.
71. Gerritsen J, Smidt H, Rijkers G, de Vos W. Intestinal microbiota in human health and disease; the impact or probiotics. *Genes Nutr* 2011; **6**: 209–40.
72. National Cancer Survivorship Initiative Vision. Available at: www.ncsi.org.uk. Accessed April 2013.
73. Whelan K, Myers C. Safety of probiotics in patients receiving nutritional support: a systematic review of case reports, randomised controlled trials, and nonrandomised trials. *Am J Clin Nutr* 2010; **91**: 678–703.

TABLE S1. Randomised controlled trials, controlled trials and case series of acute nutritional interventions in adult patients receiving pelvic radiotherapy

First Author Year Country Ref. No.	Patient details	Study	Radiotherapy treatment details		Intervention details		Efficacy outcomes (Acute)
	N recruited *N evaluated* *Male : Female* *Age*	*Study Design* *Intention*	*Dose (Gy)* *Fraction (#)* *+/- CT*	*Pelvic sites* *(% of cohort)*	*Intervention details by group (G1,G2,G3)* *Dose*	*Duration (weeks)*	*Clinical outcomes:* *Compliance / tolerance (where reported)*
Elemental formulae							
Brown 1980 UK (35)	68 recruited Evaluated NR 53 M : 15 F Age range: 29 – 69yrs	Open label RCT Preventative	Median: 50 Gy 20 # CT NR	Mixed pelvic cohort: Bladder: 50 Prostate: 21 Testis: 8 Ureter: 2 Gynaecological: 13 Colon: 4 Lymphoma: 2	G1: Low fibre diet (dose NR) G2: Low fibre diet (dose NR) with Vivonex HN elemental formula providing 900 kcals/day	Acute treatment 4/5 weeks	*Clinical:* • No significant difference between groups in mean weight loss (G1: -1.6 kg versus G2: -0.5kg) in per protocol analysis • No difference between groups in mean stool frequency per day (Gi: 4/day versus G2: 4/day) in per protocol analysis • No difference between groups (including non-compliant patients) in time to diarrhoea or use of constipating agents *Compliance / tolerance :* • 21/51 (41%) patients failed to tolerate elemental formula for entire course • Main reasons for non-compliance: potentiated nausea (32%) and unpalatability of formula (27%)
Capirci 2000 Italy (36)	677 recruited Evaluated NR Gender NR Age NR	Open label RCT Preventative	Dose NR # : NR CT NR	Mixed pelvic cohort: Post-surgical: Uterus: 34 Rectum: 65 Prostate: 1	G1: Standard diet (not defined) G2: Natural diet (not defined) with Peptinaut elemental formula providing 33% of total energy	Weeks: NR	*Clinical*: • Significant difference between groups in proportion of patients with RTOG graded toxicity (RTOG Grade 1 experienced by 25% in G1 versus 16% in G2) and (RTOG Grade 2 experienced by 27% in G1 versus 12% in G2) *p=NR* • Greater mean severe weight loss between start and end-RT experienced in G2 versus G1 (G2: weight loss -5.5kg versus G1: -3.8kg) *p=NR* • Significant difference between groups in treatment interruption due to toxicity (G1: 44/345 versus G2: 12/332) *p<0.05* • Benefit of intervention lost in patients with volume of small bowel irradiated >500cc but specific outcomes affected not specified *Compliance / tolerance :* • NR
McGough 2008 UK	50 recruited 47 evaluated 21 M : 29 F	Open label RCT	Mode: G1: 54 G2: 50.4	Mixed pelvic cohort: Endometrium: 26 Cervix : 14	G1: Habitual diet G2: Habitual diet plus elemental formula E028 Extra providing 33% of total energy	First 3 weeks of treatment	*Clinical:* • No significant difference between groups in the change in IBDQ-B score between start and end-RT (*p=0.214*) • No significant difference between groups in the change in faecal

(37)	Age range: 20 – 82 yrs	Preventive	28 – 30 # CT: G1: 28% G2: 44%	Ovary: 2 Bladder: 4 Prostate: 22 Rectum: 18 Anus: 8 Other pelvic site: 6			calprotectin levels between start and end-RT (*p=0.151*) *Compliance / tolerance :* • Mean amount of elemental formula ingested in G2 was 21% of caloric intake rather than the planned 33%
Foster et al 1980 UK (38)	32 recruited 32 evaluated 27 M : 5 F 65 yrs	Open label RCT Preventative	Median: 57 Gy 25 # CT NR	Mixed pelvic cohort: Bladder: 61 Prostate: 25 Testis: 6 Uterus: 4 Colon: 4	G1: Low fibre diet (dose NR) G2: Low fibre diet (dose NR) with Vivonex HN elemental formula providing 900 kcals/day	Acute treatment 4/5 weeks	*Clinical / physiological:* • No significant difference between groups in weight loss during treatment with both groups experiencing significant loss compared to baseline. • Rise in blood alanine, serum insulin and triglyceride, with significant falls in blood electrolytes, albumin and protein but no significant differences between groups at end-RT. *Compliance / tolerance :* • NR
Craighead 1998 Canada (39)	17 recruited (intervention) 17 evaluated 0 M : 17 F 48 yrs 45 in comparator group (non-intervention) 0 M : 45 F Age : NR	Controlled Trial with treatment matched comparator group Preventative	≥45 Gy ≥ 25 # CT NR	Gynaecological cohort: Intervention group: Post surgical radiotherapy: Cervix: 12 Endometrium: 53 Radiotherapy alone: Cervix: 35	G1: lactose-restricted, low fat (<30% kcals), low fibre (12g/day) diet G2: Vital HN elemental formula providing 33% of total energy plus lactose-restricted, low fat, low fibre diet	3 days pre-RT and during acute treatment	*Clinical:* • Increased occurrence of RTOG grade 2/3 diarrhoea in G1 patients combined with non-compliant G2 patients (55%) versus G2 compliant patients (15%) (*p<0.001*) • Increased proportion of patients in G1 requiring anti-diarrhoeal agents during acute treatment (51%) versus G2 compliant patients (15%) • No significant difference in weight loss between compliant and non-compliant patients in G2 from start to end-RT • No compliant patients in G2 with diarrhoea one year post RT versus 4/4 non-compliant patients in G2 with diarrhoea and 19/45 patients in comparator arm. *Compliance / tolerance:* • Significant level of compliance demonstrated in G2 with 13/17 patients taking required elemental dose for >80% of time (*p<0.01)*) • 80% compliance with dietary restrictions in G2 reported in patients both complying with elemental formula intake and those not complying.
McArdle 1986 Canada (40)	24 recruited (Intervention) 19 M : 5 F 64 yrs 32 retrospective comparator group 24 M : 8 F 65 yrs	Controlled Trial with retrospective (non-intervention comparator group Preventative	20 Gy 5 # CT NR	Urological cohort: Pre-surgical (prior to radical cystectomy): Bladder: 100	G1: Conventional 'in-patient' feeding with hospital food or TPN (Total Parenteral Nutrition) G2: Vital elemental formula (via intubation) comprising 100% of total energy intake	3 days pre-RT and for 5 days during radiotherapy treatment up to 24 hours prior to surgery and then post-surgically for 7 days	*Clinical:* • Significantly reduced number of patients experiencing severe diarrhoea post-operatively in G2 (0/24) versus G1 (10/32) (*p<0.001*). • Two-fold increase in number of patients with gastrointestinal symptoms in G1 versus G2 (*p<0.05*) in both pre- and post-operative periods. • Significantly earlier passage of bowel faeces and flatus in G2 versus G1 post-operatively (*p<0.001*) *Compliance / tolerance :* • NR

Low or modified fat diets							
Bye et al 1992 Norway (21)	143 recruited 129 evaluated 0 M : 143 F 51 yrs	Open label RCT Preventative	40 -52 Gy 20 – 26 # CT NR	Gynaecological cohort: Cervix: 65 Uterus: 34 Ovary: 1	G1: Regular hospital diet (fat 80g / day) G2: Low fat, low lactose diet (fat 40g / day, lactose 5g /meal	Active treatment (5 to 6 weeks)	*Clinical:* • Significantly increased frequency of loose / watery stool at end-RT in G1 (1.7 / day) versus G2 (1.1 / day) (*p<0.01*) • Significantly increased number of patients reported new onset diarrhoea during treatment in G1 (48%) versus G2 (23%) (*p<0.01*) • Significant two-fold reduction in the number of anti-diarrhoeal tablets used by G2 (mean 0.6 tablets / day) versus G1 (mean 1.1 / day) (*p<0.01*) • No significant difference in weight loss during treatment (see below) *Compliance / tolerance:* • Significant difference between groups in fat intake at week 6 (G1: 60.1g / day versus G2: 34.3 g / day (p<0.001) • Greater weight loss in G2 (mean 2.6 kg) versus G1 (mean 1.7 kg) between start-RT and end-RT
Chary 1984 Canada (25)	35 recruited 33 evaluated 23 M : 10 F 68 yrs	Double blind Placebo RCT Preventative	50 Gy 38 # CT NR	Mixed pelvic cohort: Bladder: 37 Prostate: 33 Cervix: 12 Ovary: 9 Endometrium: 9	G1: Low fat diet (40g / day) plus placebo G2: Low fat diet (40g / day) plus Cholestyramine (4g bd)	Active treatment (5 to 6 weeks)	*Clinical:* • Significantly reduced diarrhoea scale score in G2 versus G1 at weeks 4, 6 and 7 after start of RT (*p≤0.05*) • Marked absence of occurrence of diarrhoea in G2 (16/17 patients) versus G1 (9/16 patients) • No difference between groups in weight loss between start and end-RT *Compliance / Tolerance:* • Greater incidence of adverse effects due to medication in G2 with 9/17 patients reporting adverse effects including nausea and abdominal cramps.
Karlson 1989 Sweden (41)	21 recruited Evaluated NR 0 M : 21 F 64 yrs	Open label RCT Preventative	Dose NR # NR CT NR	Gynaecological cohort: Ovarian: % NR Uterus: % NR	G1: Low fat diet (20g / day) with total energy intake of 2000kcals per day G2: Low fat diet (20g / day) supplemented with high-protein MCT enriched feed plus 1000 kcals of low fat foods	Active treatment 4 weeks	*Clinical:* • Increased total energy and protein intake in G2 at 4 weeks versus G1 (mean difference of 237 kcals and 11g protein) (*p<0.05*) • No difference in change in body weight between groups between start-RT and end-RT • Reduced bowel frequency in G2 (1.6 ± 0.9 movements / day) versus G1 (2.0 ± 1.0) during treatment (*p=NR*) *Compliance / Tolerance:* • Low fat intervention 'well tolerated'
Wedlake 2012 UK (42)	117 recruited 107 evaluated 79 M : 38 F 65 yrs	Open label RCT	Median 54 Gy 30 # CT : 50%	Mixed pelvic cohort: Prostate: 38 Bladder: 9 Colorectal: 31 Anal: 2	G1: Normal fat diet with LCT ≤ 40% total energy / day G2: Modified fat diet with LCT providing ≤ 20% of total energy plus MCT providing 20% of total energy / day	Active treatment 4 weeks	*Clinical:* • No significant difference in change in IBDQ-B scores between groups from start-RT to end-RT (mean fall in IBDQ-B score all groups: -7.3 ± 0.9 points) • No significant difference in change in weight between groups from start-RT to end-RT (mean change in weight all groups: -0.6 ± 2.1 kg) • No significant difference between groups in change grip strength

		Preventive		Endometrium: 9 Cervix: 7 Ovary: 2 Vulva: 2	G3: Low fat diet with LCT ≤ 20% of total energy / day		between start and end-RT nor secondary toxicity measures including Vaizey incontinence questionnaire and RTOG toxicity score *Compliance / Tolerance:* • Reduced fat consumption in G1 resulted in mean intake of 63g LCT-derived fat / day compared to prescription amount of (mean) 95 g / day • Study failed to achieve required differential in LCT fat intake between groups which may have resulted in confounding • Self-reported 100% compliance with fat prescription in 37/40 patients (G3), 29/38 patients (G2) and 3/35 patients (G1).
Dietary fibre							
Lodge 1995 UK (43)	10 recruited 10 evaluated 0 M : 10 F Age : NR	Open label Cross over RCT Therapeutic	Dose : NR # NR CT : NR	Gynaecological cohort: Site(s): NR	G1: Standard medication (Codeine phosphate) plus low residue diet (not defined) G2: Ispaghulahusk plus low residue diet (not defined)	Intervention started on presentation of treatment induced diarrhoea	*Clinical:* • Cessation of study after 5/5 patients in G1 responded to medication versus 1/5 in G2 who responded (*p<0.004*) • Improvement in stool consistency and control following cross-over of G2 patients to G1 *Compliance / Tolerance:* • Patients in G2 reported intolerance to medication including unpalatability (3/5 patients) and difficulty swallowing (1/5 patients)
Liu 1997 Israel (44)	156 evaluated 156 M : 0 F 71 yrs	Retrospective Case series Preventive	72 Gy CT : NR	Urological cohort: Prostate: 100	All patients: Dietary advice including low residue diet (reduce whole grains, nuts and seeds), avoid alcohol and spicy foods	Active treatment 5 weeks	*Clinical:* • Side-effects of treatment reported in 17% of patients who failed to follow dietary advice throughout treatment. • 41% (64/156) patients experienced Grade 1 gastrointestinal toxicity which were 'easily managed' by dietary reinforcement. • Reduced incidence of Grade 2 gastrointestinal toxicity compared to other similar patient cohorts. *Compliance / Tolerance:* • 17% (26/156) patients reported periods of non-compliance with diet.
Murphy 2000 Canada (45)	84 recruited 60 evaluated 51 M : 9 F 65yrs (M) 60 yrs (F)	Open label RCT Preventive	65 Gy (M) 68 Gy (F) CT: NR	Mixed pelvic cohort: Prostate: 85 Gynaecological: 15	G1: Low fibre (dose NR), limited fat (dose NR) alcohol and caffeine G2: Low fibre (dose NR), limited fat (dose NR) alcohol and caffeine plus psyllium supplement (dose NR)	Active treatment 4 - 5 weeks	*Clinical:* • Incidence of diarrhoea (bespoke scale) significantly reduced in G2 versus G1 (*p=0.049*) • Severity of diarrhoea (bespoke scale) significantly reduced in G2 versus G1 (*p=0.030*) • Reduced need from anti-diarrhoea medication in G2 versus G1 (*p=NS*) *Compliance / Tolerance:* • Of the 24 patients not included in the final analysis, 21 were excluded for inaccurate, incomplete and failure to return bowel habit diaries.
McNair 2011	25 recruited 22 evaluated	Prospective case series	70 - 74 Gy 35 -37 #	Urological cohort: Prostate: 100	G1: Individualised dietary fibre and fluid prescription combined	Active treatment	*Clinical:* • Reduced fall in IBDQ score versus baseline in subgroup of patients (n=9)

UK (46)	25 M : 0 F 70 yrs	Control of organ displacement	57 – 60 Gy 19 – 20 # CT : NA		with standardised treatment scheduling	4 – 7 weeks	who achieved fibre prescription at all time-points versus those (n=11) who did not (mean fall of 19.4 points versus 27.6 points respectively) • Reduced fall in IBDQ-B score versus baseline in subgroup of patients who achieved fibre prescription versus those who did not (mean fall of 9.2 points versus 12.4 points respectively) • Mean daily bowel frequency (all patients) increased from 1.2 motions / day pre-RT to 1.7 per day at end-RT. Loose stool (Bristol Stool form 6/7) occurred on <2% of treatment days. *Compliance / Tolerance:* • No adverse effects of increased fibre consumption reported. 8/20 patients failed to achieve fibre prescription at any time-point but shortfall was <3.0 g NSP / day.
Lactose restriction							
Stryker 1978 USA (22)	24 recruited 24 evaluated 0 M : 24 F 57 yrs	Prospective case series Observational	42 – 51 Gy 25 – 30 # CT : NR	Gynaecological cohort: Cervix: 38 Endometrium: 33 Ovary: 29	G1: Habitual diet with 50g lactose challenge at start-RT & end- RT	Active treatment 5 – 6 weeks	*Clinical:* • Significantly reduced lactose absorption at one, two and three hours after lactose challenge at end-RT compared to start-RT (*p=0.02, 0,05 and 0.01*) • Significantly increased stool frequency at end-RT (3.5 / day) compared to baseline values (1.5 / day) (*p<0.001*) • Significant correlation between stool frequency at week 5 and lactose malabsorption (*p<0.05*) in all patients • Abnormal breath tests in 50% of patients at week 5 from start RT *Compliance / Tolerance:* • 7/12 patients with lactose malabsorption at week 5 experienced nausea.
Weiss et al 1982 USA (47)	30 recruited 30 evaluated Gender: NR 60 yrs	Prospective case series Observational	42 – 51 Gy 25 – 30 # CT : NR	Mixed pelvic Cohort: Endometrium: 40 Cervix: 13 Ovary: 3 Rectum: 13 Bladder: 10 Prostate: 18 Lymphoma: 3	G1: Habitual diet with 50g lactose challenge at start-RT and end-RT. Large volume of small bowel within RT field. G2: Habitual diet with 50g lactose challenge at start-RT and end-RT. Small bowel almost completely shielded.	Active treatment 5 – 6 weeks	*Clinical:* • Significantly reduced lactose absorption in G1 at week 5 of RT in comparison to week 1 of RT (*p<0.05*) versus no significant difference in lactose absorption in G2 between weeks 1 and 5. • No correlation between increase in stool frequency and change in lactose absorption in G1 or G2. *Compliance / Tolerance:* • 10/21 patients (G1) reported nausea during treatment versus 0/9 patients reporting nausea in G2.
Stryker et al 1986 USA (48)	64 recruited 53 evaluated 7 M : 57 F 58 yrs	Open label RCT Preventive	170-180 Rad 25 # CT : NR	Mixed pelvic cohort: Endometrium: 55 Cervix: 28 Vagina: 8 Prostate: 6 Ovary: 1.5 Colon: 1.5	G1: Habitual diet with 480 cc of milk / day G2: Lactose restricted diet (not defined) with calcium supplementation G3: Habitual diet with 480 cc of pre-hydrolysed milk (i.e. addition of lactase	Active treatment 5 weeks	*Clinical:* • No significant difference between groups in the number of anti-diarrhoeal tablets taken or patient-reported stool frequency. *Compliance / Tolerance:* • NR

Prebiotics, probiotics and synbiotics							
Salminen 1988 Finland (49)	24 recruited 21 evaluated 0 M : 24 F 40 – 75 yrs	Open label RCT Preventive	50 Gy to pelvic area and 80 Gy to tumour 2 Gy # CT : NR	Gynaecological cohort: Uterus: % NR Cervix: % NR	G1: Low fat, low residue, low lactose diet G2: Low fat, low residue, low lactose diet with synbiotic: 50 ml / day pre-hydrolysed milk containing $2x10^9$ CFU of Lactobacillus acidophilus and 6.5% lactulose (8g / day)	5 days prior to RT and during active treatment	*Clinical:* • Significantly reduced incidence of diarrhoea in G2 versus G1 (*p<0.01)* • Increased requirement for use of anti-diarrhoeal medication in G1 (6 permanent users) versus G2 (1 permanent user) *Compliance / Tolerance:* • Increased flatulence in G2 versus G1 but no difference between groups in incidence of vomiting, nausea, pain, appetite loss or weight loss.
Urbancsek 2001 Hungary (50)	206 recruited 205 evaluated 25% M : 75% F 28 - 86 yrs	Double blind Placebo RCT Therapeutic	Median at study entry: 50 Gy 25 # CT : NR	Mixed pelvic cohort: Uterus: %NR Ovary: % NR Prostate: % NR Rectum: % NR Other pelvic ca: % NR	G1: Placebo G2: Probiotic: $1.5x10^9$ CFU Lactobacillus rhamnosus (x3/day)	On presentation of diarrhoea during active treatment for one week	*Clinical:* • No significant difference between groups in the proportion of patients requiring use of rescue medication: G1 (48%) versus G2 (35%) • No significant difference between groups in the time before starting rescue medication: G1 (125 hours) versus G2 (138 hours) • No significant difference between groups in secondary end-points including bowel frequency, severity of diarrhoea, incidence malformed or liquid stool. • Pooled duration of diarrhoea (3.2 days) after induction of rescue medication not affected by prior treatment (G1 or G2). *Compliance / Tolerance:* • No adverse events recorded. Similar proportion of patients (n=3 / group) reported gastrointestinal symptoms or anal soreness during intervention.
Delia et al 2007 Italy (51)	490 recruited 482 evaluated Gender NR Age NR	Double blind Placebo RCT Preventative	60 – 70 Gy 32 38 # CT : NR	Mixed pelvic cohort: Colorectal: % NR Cervical: % NR	G1: Placebo G2: Probiotic (VSL#3) 450 x 10^9 CFU/g of lactobacilli (4 strains), bifidobacteria (3 strains) and streptococcus salivarius	Active treatment	*Clinical:* • Significantly increased incidence of 'radiation-induced enteritis' in G1 (124/239 patients) versus G2 (77/243 patients) (*p<0.001*) • Significantly increased severity of diarrhoea in G1 (69/124 patients with WHO grade 3 or 4 diarrhoea) versus G2 (8/77 patients) (*p<0.001*) • Significantly increased mean daily number of bowel movements in G1 (14.7±6) versus G2 (5.1±3) (*p<0.05*) • Significantly increased mean time to use of loperamide 'rescue medication' in G2 (122±8 hours) versus G1 (86±6 hours) (*p<0.001*) *Physiology:* • No adverse effects of probiotic supplementation reported during treatment or 6 months post-RT.
Giralt 2008 Spain (52)	118 recruited 85 evaluated 0 M : 118 F 60 yrs	Double blind Placebo RCT	45 – 50.4 Gy 25 – 28 # CT: Cervix	Gynaecological cohort: Endometrium: 63 Cervix: 27	G1: Placebo G2: Probiotic: liquid yoghurt presentation containing lactobacillus casei 10^8 CFU/g	1 week pre-RT and during active treatment	*Clinical:* • No significant difference in proportion of patients experiencing diarrhoea ≥ grade 3 (CTC of NCI) in G1 (15/44 patients) versus G2 (20/44 patients) • No significant difference in proportion of patients requiring rescue medication in G1 (12/41 patients) versus G2 (16/44 patients)

		Preventive	Cisplatin (40 mg /m^2) G1: 51% G2: 33%				• No significant difference between groups in the time to diarrhoea or mean of days with Bristol Stool Type of type 5, 6 or 7. • Significantly reduced time to onset of loose stool (type 6) in G1 (10 days) versus G2 (14 days) (*p=0.048*) *Compliance / Tolerance:* • Study failed to reach accrual target of 154 patients. Of the 118 patients enrolled after 3 years, 33 were excluded of which 16 exclusions were for protocol violations or non-compliance. • No adverse events related to intervention.
Chitapanarux 2010 Thailand (53)	63 recruited 63 evaluated 0 M : 63 F 50 yrs	Double blind Placebo RCT Preventative	56 Gy 28 # CT: Cervix Cisplatin (40 mg /m^2)	Gynaecological cohort: Cervix: 100%	G1: Placebo plus standard dietary recommendations for radiotherapy (not defined) and restricted 'fermented' products G2: Probiotic: One 250mg capsule qds containing 2 x 10^9 CFU Lactobacillus acidophilus plus bifidobacterium bifidum plus standard dietary and fermented product recommendations as G1	One week pre-RT and during active treatment 6 weeks	*Clinical:* • Significantly reduced severity of diarrhoea in G2 versus G1 (55, 42 and 3% for grades 1, 2 and 3 diarrhoea in G1 versus 91, 9 and 0% in G2) (*p=0.002*) • Significantly improved stool consistency in G2 versus G1 (prevalence of formed, soft and liquid stool of 0, 35 and 65% in G1 versus 3, 78 and 19% in G2 (*p<0.001*) • Significantly reduced need for anti-diarrhoeal medication in G2 versus G1 32% of patients requiring medication versus 9% respectively) (p=0.03) *Compliance / Tolerance:* • No adverse events related to probiotic administration recorded. • Patients taking <80% of study probiotic or placebo (assessed on return of receptacles) were judged to be non-compliant but included in the ITT analysis.

Table 2 - Quality analysis

Reference (a) abstract only	*Quality Criteria*																	**Total Score**
	Participants randomised?	*Adequate concealment?*	*Participants blinded?*	*Investigators blinded?*	*Placebo given?*	*Study powering with primary outcome stated?*	*Required recruitment achieved?*	*Drop-outs and withdrawals documented?*	*Study groups comparable at baseline?*	*Eligability criteria stated?*	*Appropriate efficacy measures?*	*Validated tools for assessing efficacy?*	*Appropriate (up front) definition of responder?*	*Analysis of compliance provided?*	*Adverse events documented?*	*Intolerance to intervetion documented?*	*Single dietary intervention?*	
ELEMENTAL FORMULAE																		
35. Brown 1980	yes	ns	no	no	no	no	uc	yes	yes	yes	yes	p	ns	yes	no	yes	no	7
36. Capirici 2000 (a)	yes	ns	no	ns	no	no	uc	no	ns	no	yes	yes	ns	no	yes	no	uc	4
37. McGough 2008	yes	ns	no	no	no	yes	yes	p	yes	yes	yes	yes	yes	yes	ns	p	yes	10
38. Foster 1980	yes	ns	no	ns	no	na	yes	yes	yes	yes	uc	yes	ns	p	yes	na	no	7
39. Craighead 1998	na	na	no	no	no	yes	uc	ns	p	yes	yes	p	yes	p	ns	yes	no	5
40. McArdle 1986	na	na	no	no	no	no	no	ns	p	yes	yes	p	ns	ns	yes	ns	yes	4
LOW OR MODIFIED FAT																		
21. Bye 1992	yes	ns	no	no	no	no	uc	yes	yes	yes	yes	p	no	yes	yes	yes	no	8
25. Chary 1984	yes	ns	yes	yes	yes	no	uc	yes	yes	yes	yes	p	yes	no	yes	yes	yes	12
41. Karlson 1989 (a)	yes	ns	no	no	no	no	uc	ns	p	yes	yes	uc	ns	no	no	no	no	3
42. Wedlake 2012	yes	ns	no	no	no	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	13
FIBRE																		
43. Lodge 1995	yes	ns	ns	ns	no	no	no	yes	ns	yes	yes	yes	yes	no	yes	yes	yes	9
44. Lui 1997	no	na	na	no	na	no	uc	na	na	yes	yes	yes	yes	p	yes	no	no	5
45. Murphy 2000	yes	ns	no	no	no	no	yes	yes	yes	yes	yes	p	no	no	yes	yes	no	8
46. McNair 2011	no	na	na	no	na	yes	yes	yes	na	yes	yes	yes	yes	yes	yes	yes	yes	11
LACTOSE																		
22. Stryker 1978	no	na	na	no	no	no	uc	na	na	yes	yes	yes	yes	n/a	n/a	yes	yes	6
47. Weiss 1982	no	na	no	ns	no	no	uc	na	na	p	yes	yes	p	na	n/a	yes	yes	4
48. Stryker 1986	yes	ns	no	no	no	no	uc	yes	p	yes	yes	yes	no	p	no	p	yes	6
PROBIOTICS AND SYNBIOTICS																		
49. Salminen 1988	yes	ns	no	ns	no	no	uc	yes	ns	yes	yes	p	no	p	p	yes	no	5
50. Urbancsek 2001	yes	yes	yes	yes	yes	p	yes	yes	yes	yes	p	p	yes	yes	yes	yes	yes	14
51. Delia 2007	p	ns	p	p	p	p	uc	yes	ns	yes	yes	yes	no	no	yes	no	uc	5
52. Giralt 1986	yes	ns	yes	yes	yes	yes	no	yes	no	yes	yes	yes	yes	p	yes	no	yes	12
53. Chitapanarux 2010	yes	ns	yes	yes	yes	p	yes	yes	yes	yes	yes	yes	no	yes	yes	ns	uc	12

KEY: Yes: satisfies criteria, No: does not satisfy criteria, p: partly satisfies criteria, uc: unclear if criteria satisfied, ns: not stated in article, na: Criteria not applicable